https://doi.org/10.56871/PED.2025.64.82.009 UDC 504.054+615.9+577.121+612.017

Principles of functioning of the immunotoxicant metabolism system. Part 2: the second and third phases of biotransformation

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ABSTRACT

Biotransformation and metabolism of immunotoxicants is a complex and multi-stage process. This part of the review is devoted to the second and third stages of biotransformation of immunotoxicants, which are classified as ecotoxicants and are drugs. In second phase, partially transformed xenobiotic molecules are conjugated with certain intracellular compounds, such as glutathione, and converted into relatively safe hydrophilic metabolites of the original xenobiotic. The review describes in detail the enzyme systems that carry out biotransformation reactions of second phase. The enzymes of this biotransformation phase ultimately allow for a significant increase in the hydrophilicity of biotransformed metabolites for their subsequent excretion from the body and carry out the final detoxification of xenobiotics, including those with immunotoxicity. The known data on the localization of various isoforms of enzymes and their substrate specificity are summarized. Some reactive products of the second phase of xenobiotic biotransformation, which may be toxic to cells, are presented.

The third phase of biotransformation is the active secretion of immunotoxicants and their metabolites into urine or bile, which is carried out by proteins belonging to the superfamily of secondary membrane-bound MFS (Major Facilitator Superfamily) transporters. Transporters of the third phase are present in many tissues, including the liver, intestines, kidneys and brain, where a barrier is provided against the penetration of xenobiotics into the body. These biomolecules play an important role in regulating the absorption, distribution and excretion of many drugs and immunotoxic xenobiotics, as well as participate in the removal of newly formed products of the second phase of biotransformation from cells.

Keywords: xenobiotics, immunotoxicants, second phase of biotransformation, third phase of biotransformation

To cite this article
Kashuro V.A., Kozlov V.K., Batotsyrenova E.G., Vasiliev A.G., Nevzorova T.G., Litvinenko L.A., Kuzmina N.V. Principles of functioning of the immunotoxicant metabolism system. Part 2: the second and third phases of biotransformation. *Pediatrician (St. Petersburg)*. 2025;16(5):79–99. (In Russian). https://doi.org/10.56871/PED.2025.64.82.009.

Submitted: 17.09.2025 **Accepted: 10.11.2025** **Published online: 30.01.2026**

ISSN 2587-6252 (Online)

https://doi.org/10.56871/PED.2025.64.82.009 УДК 504.054+615.9+577.121+612.017

Принципы функционирования системы метаболизма иммунотоксикантов. Часть 2: вторая и третья фазы биотрансформации

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РЕЗЮМЕ

Биотрансформация и метаболизм иммунотоксикантов — сложный и многостадийный процесс. Данная часть обзора посвящена второй и третьей стадиям биотрансформации иммунотоксикантов, являющихся экотоксикантами и лекарственными веществами. Во второй фазе частично трансформированные молекулы ксенобиотика конъюгируются с некоторыми внутриклеточными соединениями, такими как глутатион, и превращаются в относительно безопасные гидрофильные метаболиты исходного ксенобиотика. В обзоре подробно описаны ферментные системы, осуществляющие реакции второй фазы биотрансформации. Ферменты этой фазы биотрансформации в конечном итоге позволяют значительно увеличить гидрофильность биотрансформированных метаболитов для их дальнейшей экскреции из организма и осуществляют окончательную детоксикацию ксенобиотиков, в том числе обладающих иммунотоксичностью. Обобщены известные данные по локализации различных изоформ ферментов и их субстратной специфичности. Представлены некоторые реактивные продукты второй фазы биотрансформации ксенобиотиков, которые могут быть токсичны для клеток.

Третья фаза биотрансформации представляет собой активную секрецию иммунотоксикантов и их метаболитов в мочу или желчь, которая осуществляется белками, относящимися к суперсемейству вторичных мембраносвязанных переносчиков MFS (Major Facilitator Superfamily). Транспортеры третьей фазы присутствуют во многих тканях, включая печень, кишечник, почки и мозг, где обеспечивается наличие барьера против проникновения в организм ксенобиотиков. Эти биомолекулы играют важную роль в регуляции абсорбции, распределения и экскреции многих лекарств и иммунотоксичных ксенобиотиков, а также участвуют в выведении из клеток вновь образованных продуктов второй фазы биотрансформации.

Ключевые слова: ксенобиотики, иммунотоксиканты, вторая фаза биотрансформации, третья фаза биотрансформации

Как цитировать
Кашуро В.А., Козлов В.К., Батоцыренова Е.Г., Васильев А.Г., Невзорова Т.Г., Литвиненко Л.А., Кузьмина Н.В. Принципы функционирования системы метаболизма иммунотоксикантов. Часть 2: вторая и третья фазы биотрансформации. *Педиатр*. 2025;16(5):79–99. https://doi.org/ 10.56871/PED.2025.64.82.009.

Рукопись получена: 17.09.2025 **Рукопись одобрена: 10.11.2025** **Опубликована online: 30.01.2026**

ISSN 2079-7850 (Print)

INTRODUCTION

After completion of phase I biotransformation of chemical compounds, their metabolites that were not included in the metabolic pathways of oxidation or biosynthesis may undergo phase II biotransformation reactions and then excreted as conjugates into the GIT and urine [9].

The mechanisms, chemical and enzymatic reactions of phase II xenobiotic biotransformation are associated with the covalent binding of xenobiotic metabolites formed during phase I biotransformation to endogenous molecules specialized for their elimination. The result is a hydrophilic conjugate that is excreted from the body. Phase II reactions are called derivatization or conjugation reactions.

Phase II biotransformation of xenobiotics includes glucuronidation, sulfation, acetylation, methylation, glutathionylation, and binding with amino acids such as glycine, taurine, glutamic acid, as well as the transformation of epoxides into dihydriols with the participation of epoxide hydrolases. The cofactors involved in these reactions are generated during phase I metabolism, with the exception of methylation and acetylation reactions. A general overview of phase II reactions is presented in Table 1.

The main organ where the second phase of xenobiotic metabolism occurs (as in the first phase) is the liver, but the levels of some enzymes involved in biotransformation are quite high in the GIT, gonads, lungs, brain, and kidneys [10]. Phase II reactions usually proceed much faster than phase I reactions, so the total rate of transformation and elimination of a xenobiotic depends largely on the rate at which the phase I reaction proceeds.

ENZYMATIC SYSTEMS OF THE SECOND PHASE OF BIOTRANSFORMATION OF XENOBIOTICS AND THEIR FUNCTIONAL SPECIALIZATION

Enzymes involved in the second phase of biotransformation include: uridine diphosphate glucuronyltransferase (UGT), sulfotransferase, N-acetyltransferases, glutathione-S-transferases, quinone reductases, cysteine conjugating lyases, and other enzymes.

The enzymes of this phase of biotransformation ultimately significantly increase the hydrophilicity of biotransformed metabolites for their further excretion from the body and carry out the final detoxification of xenobiotics, including immunotoxicants [4]. Most of the enzymes of the second phase of biotransformation are localized in the cytosol of cells, except for UGT, which is microsomal enzyme.

Table 2 presents the functional characteristics of the main enzymes of the second phase of xenobiotic biotransformation.

Table 1. Characteristics of the main conjugation reactions of xenobiotics [13]
Таблица 1. Характеристика основных реакций конъюгации ксенобиотиков [13]

Реакция / Reaction	Присоединяемый агент / Attachment agent	Функциональная группа ксенобиотика / Functional group of xenobiotic
А. Реакции, протекающие при участии активированных форм присоединяемых агентов/ A. Reactions occurring with the participation of activated forms of attached agents		
Конъюгация с глюкуроновой кислотой / Conjugation with glucuronic acid	Уридилдифосфоглюкуроновая кислота/ Uridyl diphosphoglucuronic acid	OH; –COOH; NH_2; $–NR_2$; –SH; –CH
Конъюгация с глюкозой / Conjugation with glucose	Уридилдифосфо-глюкоза / Uridyl diphospho-glucose	–OH; –SH; COOH; =NH
Сульфатирование / Sulfation	3’-фосфоаденозин-5’-фос- фосульфат (ФАФС) / 3’-phosphoadenosine-5’-phosphosulfate (PAPS)	–OH; $–NH_2$; –SH
Метилирование / Methylation	S-аденозилметионин / S-adenosylmethionine	–OH; $–NH_2$
Ацетилирование / Acetylation	Ацетил КоА / Acetyl CoA	–OH; $–NH_2$
Детоксикация цианида / Cyanide detoxification	Сульфон-сульфид / Sulfone sulfide	–CN
Б. Реакции, протекающие при участии активированных форм ксенобиотиков / B. Reactions involving activated forms of xenobiotics		
Конъюгация с глутатионом / Conjugation with glutathione	Глутатион / Glutathione	Ареноксиды; эпоксиды; галогенированные алкильные и арильные углеводороды / Arene oxides; epoxides; halogenated alkyl and aryl hydrocarbons
Конъюгация с аминокислотой / Conjugation with an amino acid	Глицин; глутамин; орнитин; таурин; цистеин / Glycine; glutamine; ornithine; taurine; cysteine	–COOH

Table 2. Characteristics of the main enzymes of the second phase of xenobiotic biotransformation [11, 57]
Таблица 2. Характеристика основных ферментов второй фазы биотрансформации ксенобиотиков [11, 57]

Фермент / Enzyme	Локализация / Localization	Функция / Function
УДФ-глюкуронилтрансферазы / UDP-glucuronyl transferases	Микросомы гепатоцитов / Hepatocyte microsomes	Глюкуронирование билирубина и ксенобиотиков / Glucuronidation of bilirubin and xenobiotics
Глутатион-S-трансферазы / Glutathione-S-transferases	Цитозоль и микросомы гепатоцитов / Cytosol and microsomes of hepatocytes	Конъюгация с глутатионом / Conjugation with glutathione
N-ацетилтрансфераза / N-acetyltransferase	Цитозоль гепатоцитов / Hepatocyte cytosol	Ацетилирование ксенобиотиков / Acetylation of xenobiotics
Сульфонтрансферазы / Sulfone transferases	Цитозоль гепатоцитов / Hepatocyte cytosol	Сульфатирование гормонов (тиреоидные и стероидные гормоны, катехоламины) и ксенобиотиков / Sulfation of hormones (thyroid and steroid hormones, catecholamines) and xenobiotics

ENZYMATIC GLUCURONIDATION REACTIONS: FUNCTIONAL SPECIALIZATION OF ENZYMES, INTERMEDIATE PRODUCTS (METABOLITES) OF REACTIONS AND THEIR ACTIVITY

The enzymatic reactions of glucuronidation are carried out by a group of enzymes known as glucuronyltransferases. Glucuronyltransferases catalyze the conjugation of xenobiotics or their metabolites with glucuronic acid via UDP-glucuronyltransferase (UGT) [10, 30]. This is the main route of biotransformation of xenobiotics in many mammalian species, with the exception of the cat family. Uridine diphosphoglucuronic acid participates as a cofactor in this reaction. UGT has been identified in the endoplasmic reticulum of liver cells and other tissues (kidneys, small intestine, spleen, skin, brain, etc.).

Glucuronidation typically occurs at electron-rich nucleophilic atoms of oxygen, nitrogen, or sulfur. The substrates for UGT are molecules of chemical compounds that have carboxylic, alcohol, or phenolic functional groups (the reaction produces the corresponding O-glucuronic esters), primary or secondary amino groups (N-glucuronides are formed) or a free sulfhydryl group (S-glucuronides are formed). Glucuronic conjugates are polar compounds that are soluble in water and are readily excreted in urine or bile.

The glucuronidation of xenobiotics by liver microsomes can be stimulated by detergents, which disrupt the lipid bilayer, allowing UGT greater access to uridine diphosphate glucuronic acid. However, high detergent concentrations may inhibit UGT activity by preventing the enzyme from interacting with phospholipids.

UGT catalyzes the glucuronidation of various xenobiotics, including immunotoxicants. Chemical compounds that undergo glucuronidation include: simple and complex esters; alcohols; substances containing carboxyl, carbamoyl, thiol, carbonyl, and nitro groups. The glucuronidation of toxicants in the body is usually a component of the metabolic transformations of xenobiotics that ensure their detoxification. However, endogenous compounds such as bilirubin, steroid and thyroid hormones can also be substrates for UGT.

In rare cases, glucuronidation can increase the toxicity of a xenobiotic. For example, aromatic amines such as 2-aminonaphthalene and 4-aminobiphenyl undergo N-hydroxylation in the liver, followed by N-glucuronidation of the N-hydroxy metabolite. N-glucuronides pass through the renal filter into the bladder cavity and are hydrolyzed to the corresponding carcinogenic N-hydroxyarylamines at acidic urine pH values. In this case, the increase in xenobiotic toxicity is secondary, and the activation of the xenobiotic glucuronidation reaction may contribute to the development of bladder cancer [14].

Glucuronidation of certain chemical compounds leads to the bioactivation of carcinogens. Glucuronides with procarcinogenic properties include N-glucuronide 4-aminobiphenyl, N-glucuronide N-acetylbenzidine, O-glucuronide-4-([hydroxymethyl]-nitrosamino)-1-(3-pyridyl)-1-butanone. During the first phase of biotransformation, oxidation occurs at the nitrogen atom, followed by conversion to N-glucuronides. Once in the intestine with bile, the conjugates are broken down by glucuronidase in the microflora and ultimately converted into highly reactive electrophiles — N-acetoxyarylamines. These compounds are thought to play a significant role in the development of colon cancer in humans [2].

FERMENTATIVE SULFATION REACTIONS: FUNCTIONAL SPECIALIZATION OF ENZYMES, INTERMEDIATE PRODUCTS (METABOLITES) OF REACTIONS AND THEIR ACTIVITY

Along with glucuronidation reactions, the metabolites of many xenobiotics undergo biotransformation through sulfate conjugation [1]. Sulfotransferases are responsible for this stage of biotransformation and metabolism of xenobiotics. Enzymes of this group have been identified in the cells of the liver, kidneys, intestines, lungs, and brain. The cofactor for sulfate

conjugation reactions is the active form of sulfuric acid, 3'-phosphoadenosine-5'-phosphosulfate (PAPS), which is synthesized in the body from adenosine triphosphate (ATP) and inorganic sulfate. A deficiency of PAPS due to a lack of sulfate or genetic defects leading to insufficient activity of the enzymes that catalyze its formation can disrupt the processes of detoxification of both xenobiotics and the degradation of endogenous compounds [15].

Sulfate conjugation involves the transfer of a sulfate group (SO^{3-}) from PAPS to a biotransformable xenobiotic [1]. The substrates of this reaction are alcohols and phenols, which are often the products of phase I biotransformation and metabolism of xenobiotics and drugs. Xenobiotics that do not require prior activation by first-phase enzymes for their effective metabolism include primary and secondary alcohols, bile acids, catechols, and some aromatic amines (e.g., aniline and 2-aminonaphthalene). Such chemical compounds are conjugated with PAPS to form the corresponding sulfamates.

N-hydroxyarylamines are also substrates for sulfotransferases. In all cases, the reaction involves a nucleophilic attack of oxygen or nitrogen atoms on the sulfur atom in PAPS with cleavage of the phosphosulfate bond. Sulfate conjugates are highly water-soluble esters of sulfuric acid, which are excreted mainly in the urine. Metabolites excreted in bile can be hydrolyzed by arylsulfatases present in the intestinal microflora, which contributes to their enterohepatic circulation.

Sulfotransferases are divided into two large groups depending on their localization: membrane-associated and cytosolic. Membrane-associated sulfotransferases are present in both the endoplasmic reticulum and lysosomes, where they are mainly involved in the metabolism of endogenous peptides, proteins, glycosaminoglycans, and lipids, but are not involved in the biotransformation of xenobiotics. Cytosolic sulfotransferases are involved in the metabolism of a large number of different xenobiotics, including drugs, as well as endogenous substrates (steroid hormones, catecholamines, eicosanoids, vitamins A and D, etc.). Some sulfate conjugates undergo further biotransformation. Sulfation promotes the catabolism of thyroxine and triiodothyronine and may determine the rate of elimination of thyroid hormones. During intrauterine development, sulfotransferases are one of the main pathways of biotransformation, since UDP-glucuronyltransferase is still inactive in the fetus until the 20th week [15].

In general, this biotransformation pathway is highly specific but metabolically low-capacity. The relatively low concentration of PAPS in the cell (about 75 μM, compared to a concentration of UDP-glucuronic acid of about 350 μM) limits the ability to sulfate xenobiotics.

Some xenobiotics are substrates for both sulfotransferases and UDP-glucuronosyltransferases. Substrate concentration, cofactor availability, and certain other conditions influence the choice of the preferred metabolic pathway for a particular chemical compound. For example, the relative content of paracetamol biotransformation products during its metabolism depends on the dose of the administered drug: at low doses, sulfate conjugates predominate in the metabolic products, and as the dose increases, this metabolic pathway becomes saturated and, possibly due to the inhibition of sulfotransferase activity, the relative amount of sulfate conjugates in the metabolic products decreases compared to glucuronic conjugates [16].

Four families of sulfotransferases (SULT1, SULT2, SULT4, and SULT6) and about 40 isoenzymes encoded by 10 genes have been identified in the human body [15]. Based on data on the homology of amino acid sequences of specific isoenzymes and their groups, the sulfotransferase superfamily is divided into a number of subfamilies: 1A, 1B, 1C, 1E, 2A, 2B, etc. (Table 3).

Taking into account substrate specificity, sulfotransferases are divided into the following classes:

- arylsulfotransferases are capable of sulfating many xenobiotics with a phenolic residue;
- alcohol sulfotransferases are capable of metabolizing primary and secondary alcohols, including nonaromatic hydroxysteroids;
- estrogen sulfotransferases are capable of metabolizing aromatic hydroxysteroids;
- tyrosine sulfotransferases are capable of metabolizing tyrosine, methyl esters, and bile acids.

Three types of sulfotransferases have been found in the cytosolic fraction of human hepatocytes: one steroid/bile sulfotransferase, or dehydroepiandrosterone sulfotransferase (DHEA-ST), and two isoenzymes of phenolic sulfotransferase. Phenolic sulfotransferases differ from each other in terms of thermostability — one form of the enzyme is thermostable, while the other is thermolabile. A study of the role of sulfotransferases in the bioactivation of 4-aminobiphenyl showed that N-OH-aminobiphenyl sulfotransferase activity in liver and intestinal cells correlated with the activity of the thermostable form of sulfotransferase, but not with the activity of the thermolabile DHEA-ST form [16].

The isoenzymes of the SULT1 subgroup play the most important role in the sulfation of drugs and their metabolites, with SULT1A1 and SULT1A3 being considered particularly important. The marker substrate for isoenzymes belonging to the SULT1 subgroup is 4-nitrophenol.

Endogenous substrates of SULT1A1 include 17β-estradiol, while exogenous substrates include drugs such as minoxidil, acetaminophen, morphine,

Table 3. Isoforms of the sulfotransferase family and the drugs they metabolize [15]

Таблица 3. Изоформы семейства сульфотрансфераз и метаболизируемые ими лекарственные средства [15]

Семейство / Family	Ген / Gene	Функция / Function	Хромосомная локализация / Chromosomal localization	Субстраты / Substrates
SULT1	SULT1A1	Сульфирование катехоламинов и других нейротрансмиттеров, фенолов, спиртов и аминов / Sulfation of catecholamines and other neurotransmitters, phenols, alcohols and amines	16p11.2	Парацетамол, миноксидил / Paracetamol, minoxidil
	SULT1A2			Премарин / Premarin
	SULT1A3			Парацетамол, морфин, тапентадол, трамадол / Paracetamol, morphine, tapentadol, tramadol
	SULT1A4			Парацетамол, морфин/ Paracetamol, morphine
	SULT1B1	Коньюгирование тиреоидных гормонов, фенолов, бензиловых спиртов / Conjugation of thyroid hormones, phenols, benzyl alcohols	4q13.3	Тироксин / Thyroxine
	SULT1C2	Метаболизм фенолов / Metabolism of phenols	2q12.3	Парацетамол, морфин / Paracetamol, morphine
	SULT1C3	Метаболизм дофамина, других катехоламинов и биогенных аминов / Metabolism of dopamine, other catecholamines and biogenic amines		Адреналин / Adrenaline
	SULT1C4			Доцетаксел / Docetaxel
	SULT1E1	Метаболизм эстрогенов / Estrogen metabolism	4q13.3	Эстриол / Estriol
SULT2	SULT2A1	Сульфирование стероидов и желчных кислот в печени и надпочечниках / Sulfation of steroids and bile acids in the liver and adrenal glands	19q13.33	Урсосан / Ursosan
	SULT2B1	Конъюгирование дегидроэпиандростерона (ДГЭА) / Conjugation of dehydroepiandrosterone (DHEA)		Циторабин, флударабин, гемтузумаб, озогамицин, идарубицин / Cytorabine, fludarabine, gemtuzumab, ozogamicin, idarubicin
SULT4	SULT4A1	Изоформа, специфичная для центральной нервной системы, обеспечивает метаболизм нейротрансмиттеров/ The central nervous system specific isoform mediates the metabolism of neurotransmitters	22q13.31	Адреналин / Adrenaline
SULT6	SULT6B1	Метаболизм тироксина / Thyroxine metabolism	2p22.2	Тироксин / Thyroxine

salicylamide, isadrine, and others. SULT1A3 catalyzes the sulfation reactions of monoamines with phenolic radicals: dopamine, serotonin, norepinephrine [17].

In general, sulfation as a biotransformation pathway is usually effectively accompanied by a decrease in the pharmacological activity and toxicity of xenobiotics. However, in some cases, when foreign compounds are metabolized by enzymatic sulfation, the toxicity of the metabolites exceeds that of the original xenobiotic, since some sulfate conjugates are chemically unstable and degrade, forming strong electrophilic derivatives with high reactivity. Thus, sulfo-conjugation is a necessary step in the activation of many chemical compounds that are procarcinogens (acetylaminofluorene, arylamines, and other procarcinogens). The metabolites of many N-hydroxyarylamines and hydroxamic acids formed in the sulfo-conjugation reaction also have a mutagenic effect [17].

ENZYMATIC ACETYLATION REACTIONS: FUNCTIONAL SPECIALIZATION OF ENZYMES, NTERMEDIATE PRODUCTS (METABOLITES) OF REACTIONS AND THEIR ACTIVITY

The acetylation reaction, or conjugation with acetic acid, which is considered one of the most evolutionarily ancient reactions of biotransformation of chemical compounds, is catalyzed by the enzyme N-acetyltransferase. In addition to N-acetyltransferase, coenzyme A also participates in the enzymatic acetylation reactions of chemical compounds. In the human body, the intensity of acetylation reactions is influenced by biochemical processes involving pantothenic acid,

pyridoxine, thiamine, lipoic acid, as well as processes associated with the activation of β_2-adrenoreceptors. Acetylation depends on the functional state of the liver and other organs whose tissue cells contain N-acetyltransferase.

Two isoenzymes of N-acetyltransferase have been identified and isolated — NAT1 and NAT2, which carry out N- and O-acetylation of aromatic and heterocyclic amines and hydrazines, including many carcinogens [24, 57]. NAT1 and NAT2 are similar in structure (depending on the species of the isoenzymes, 79–95% homology of amino acids in the structure of the molecules of these isoenzymes has been found), but they have substrate specificity and different levels of activity in different tissues.

NAT isoenzymes are cytosolic enzymes found in hepatocytes and cells of many other tissues in most mammalian species (except for foxes and dogs, which are incapable of N-acetylation of xenobiotics). NAT1 in adults is found in the liver, gallbladder, GIT, blood cells, placenta, skin, skeletal muscle, mammary gland, prostate, and lungs. NAT2 is mainly present in the liver and small intestine. In addition, NAT1 is found in newborns in the lungs, liver, and adrenal glands, while NAT2 activity only becomes apparent by the end of the first year of life [15].

N-acetylation is the main route of biotransformation of aromatic amines, including drugs containing a hydrazine group (R-N-NH_2). In the N-acetylation reaction, aromatic amines are converted to aromatic amides (R-NH-$COCH_3$) or hydrazides (R-NH-NH-$COCH_3$), respectively [13]. Primary aliphatic amines rarely undergo N-acetylation. An exception is the sequence of biochemical transformations in which cysteine conjugates are formed from glutathione conjugates, from which, in turn, mercapturic acid is formed by N-acetylation in the kidneys.

Many N-acetylated metabolites are less soluble in water than the parent compounds. However, in some cases, such as the metabolism of isoniazid, N-acetylation prior to excretion facilitates the elimination of isoniazid metabolites in the urine (Fig. 1).

More than 20 allelic variants of the *NAT2* and *NAT1* genes are known, which differ in activity by a factor of ten. Mutations in the N-acetyltransferase loci result in either a slow acetylation phenotype (decreased enzyme activity or stability) or a rapid acetylation phenotype (increased enzyme activity) [2].

Slow acetylators are characterized by an increase in the toxic effect of xenobiotics metabolized with the participation of the enzyme, in particular carcinogenic substances contained in tobacco smoke, exhaust gases, etc., which can contribute to a varying predisposition to malignant neoplasms. Inactivating mutations in the *NAT2* gene are associated with susceptibility

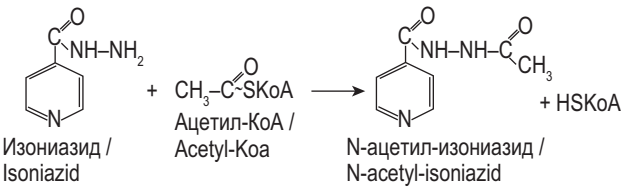


Fig.1. Isoniazid acetylation scheme [15]

Рис. 1. Схема ацетилирования изониазида [15]

to bladder cancer (the risk of developing it increases 3-fold). In rapid acetylators, occupational bladder cancer induced by 2-naphthylamine and benzidine develops significantly less frequently than in slow acetylators [15].

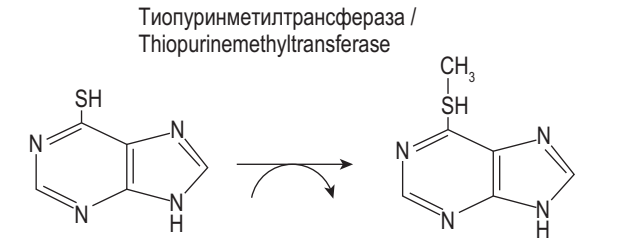
ENZYMATIC METHYLATION REACTIONS: FUNCTIONAL SPECIALIZATION OF ENZYMES, INTERMEDIATE PRODUCTS (METABOLITES) OF REACTIONS AND THEIR ACTIVITY

In the metabolism of xenobiotics, enzymatic methylation reactions are mediated by the activity of methyltransferases. Methyltransferases participate in the methylation of chemical compounds whose molecules contain hydroxyl, sulfhydryl, and amino groups [10, 18]. Thus, phenols, amines, sulfur-containing compounds, thiol poisons (mercury, lead, arsenic, tin, etc.) and some endogenous substances undergo methylation. As a result of methylation, the corresponding O-, N- and S-methyl conjugates are formed. S-adenosylmethionine, which is formed by the interaction of methionine with ATP and is a substrate for about 50 methyltransferases, acts as a methyl group donor.

Compounds containing phenolic groups undergo O-methylation. Under the influence of enzymes (O-methyltransferases), the methyl group attaches to the oxygen atoms of phenolic hydroxyls. In addition to the coenzyme, the presence of magnesium ions or other divalent metals is required for the methylation reaction of phenols. Compounds containing a single phenolic group are not methylated, even in the presence of these enzymes.

During N-methylation, under the influence of N-methyltransferase, a methyl group attaches to the nitrogen atoms of endogenous metabolites or metabolites of foreign compounds. Some foreign compounds containing thiol groups are also methylated in the body. In this case, in the presence of enzymes (S-methyltransferases), the methyl group is transferred to sulfur atoms undergoing biotransformation of metabolites, with the formation of the corresponding S-methyl derivatives of these compounds.

Methylation of xenobiotics, compared to other conjugation reactions, has one feature, which is that the addition of a methyl group does not result in the



6-меркаптопурин / 6-mercaptopurine

6-метилмеркаптопурин / 6-methylmercaptopurine

Ado-Met — S-аденозил-L-метионин / S-adenosyl-L-methionine
Ado-Hcy — S-аденозил-L-гомоцистеин / S-adenosyl-L-homocysteine

Fig. 2. 6-Mercaptopurine methylation catalysis [15]
Рис. 2. Катализ метилирования 6-меркаптопурина [15]

formation of polar metabolites, but instead eliminates the extremely reactive SH and NH groups of the preceding participants in biotransformation, which neutralizes their high reactivity. Thus, thiopurine methyltransferase catalyzes S-methylation in the metabolism of cytostatics (6-mercaptopurine, azathioprine, and thioguanine) (Fig. 2), preventing the formation of active metabolites — thioguanine nucleotides. Thiopurine methyltransferase deficiency leads to an increase in the concentration of these active metabolites, causing life-threatening myelo- and immunosuppression, which requires a several-fold reduction in the dose of these cytostatics during chemotherapy [34].

Among endogenous substances, the following are metabolized with the participation of the enzyme catechol-O-methyltransferase: adrenaline, noradrenaline, dopamine; phenol-O-methyltransferase — tyrosine, and S-adenosyl-methyltransferase — histamine [15].

ENZYMATIC GLUTATHIONYLATION REACTIONS: FUNCTIONAL SPECIALIZATION OF ENZYMES, INTERMEDIATE PRODUCTS (METABOLITES) OF REACTIONS AND THEIR ACTIVITY

Glutathione S-transferases (GSTs) are involved in glutathionylation enzymatic reactions. These enzymes catalyze the conjugation of xenobiotics with glutathione [5, 12]. Glutathione is a tripeptide consisting of glycine, cysteine, and glutamic acid, which is linked to cysteine via a γ-carboxyl group (Fig. 3). As a result of an enzymatic reaction involving GST, a thioester of the compounds participating in the reaction is formed.

There are three superfamilies of glutathione-S-transferases: cytosolic, mitochondrial, and microsomal. Cytosolic glutathione-S-transferases are divided into 13 classes (alpha, beta, delta, epsilon, zeta, theta, mu, nu, pi, sigma, tau, phi, and omega). Mitochondrial glutathione-S-transferases belong to the kappa class (GSTK). Microsomal glutathione S-transferases are

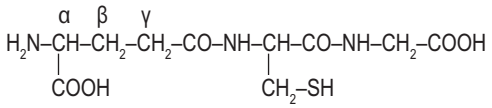


Fig. 3. Structure of glutathione (picture from the Internet)
Рис. 3. Структура глутатиона (рисунок из Интернета)

also known as MAPEG (membrane-associated proteins of eicosanoid and glutathione metabolism). The highest GST activity is observed in the liver, kidneys, brain, heart, lungs, and GIT [7]. 95% of the total enzyme content is localized in the cytoplasm and about 5% in the endoplasmic reticulum of cells.

The substrates for GST are usually hydrophobic compounds containing an electrophilic atom. Substrates for glutathione conjugation can be divided into two groups: 1) sufficiently electrophilic chemical compounds that are capable of direct conjugation with glutathione; 2) chemical compounds that require activation before the conjugation reaction can begin. The second group of compounds includes oxiarenes, alkene epoxides, nitronium ions, carbocation ions, and free radicals [14].

Conformationally, all GSTs have a similar structure and are dimers composed of a combination of two identical or non-identical subunits. GSTs form a superfamily of multifunctional isoenzymes that contribute to detoxification processes. Various mechanisms are involved in the detoxification process, including: 1) non-catalytic binding of certain reactive xenobiotics to glutathione; 2) catalytic inactivation of a wide range of xenobiotics through conjugation with reduced glutathione (GSH); 3) glutathione peroxidase activity, which restores lipid and DNA hydroperoxides [17].

The most important for the metabolism of immunotoxincants are GST isoenzymes belonging to the alpha, theta, mu, and pi classes (Table 4), encoded by *GST* genes, among which the *GSTM1* gene plays an important role in the inactivation of carcinogens. All five genes, *GSTM1, GSTM2, GSTM3, GSTM4*, and *GSTM5* are located on 1p13.3 [15].

GST isoenzymes play an important role in the metabolism of carcinogens, lipids, free radical oxidation products, catecholestrogen metabolism, and detoxification of aflatoxin B1-8,9-epoxide. Human liver GST has catalytic activity toward the reactive metabolite of benz(a)pyrene, benz(a)pyrene-4,5-oxide. In addition to the metabolism of carcinogens and other xenobiotics, GST isoenzymes are involved in the biosynthesis of biologically active molecules, including leukotrienes and prostaglandins, as well as in the binding and biotransformation of bilirubin and steroid hormones (in particular, *in vivo*, GST isoenzymes ensure the transport of these endogenous compounds). GST isoenzymes inhibit the activity of lipid peroxidation (LPO) products and

Table 4. Isoforms of the glutathione-S-transferase family and the substrates they metabolize [15]

Таблица 4. Изоформы семейства глутатион-S-трансфераз и метаболизируемые ими субстраты [15]

Ген / Gene	Функция / Function	Хромосомная локализация / Chromosomal localization	Субстраты / Substrates
GSTA1	Метаболизм эндогенных продуктов окислительного стресса и экзогенных соединений, включая ЛС, канцерогены, иммунотоксиканты и другие токсины / Metabolism of endogenous oxidative stress products and exogenous compounds, including drugs, carcinogens, immunotoxicants and other toxins	6p12.2	Цисплатин, циклофосфамид, доксорубицин, ритуксимаб, винкристин, бисульфан, преднизолон / Cisplatin, cyclophosphamide, doxorubicin, rituximab, vincristine, bisulfan, prednisolone
GSTT1		22q11.23	Клозапин, иматиниб, цисплатин, изониазид, этамбутол, пиразинамид, рифампин / Clozapine, imatinib, cisplatin, isoniazid, ethambutol, pyrazinamide, rifampin
GSTM1		1p13.3	Цисплатин, оксалиплатин, блеомицин, доксорубицин, винбластин, бисульфан, невирапин, сульфаметоксазол, триметоприм, клозапин, этамбутол, пиразинамид, рифампин / Cisplatin, oxaliplatin, bleomycin, doxorubicin, vinblastine, bisulfan, nevirapine, sulfamethoxazole, trimethoprim, clozapine, ethambutol, pyrazinamide, rifampin
GSTM3			Оланзапин, цисплатин, циклофосфамид / Olanzapine, cisplatin, cyclophosphamide
GSTP1		11q13.2	Циклофосфамид, эпирубицин, фторурацил, оксалиплатин, цисплатин, метотрексат, доксорубицин, блеомицин, этопозид, изониазид, рифампин / Cyclophosphamide, epirubicin, fluorouracil, oxaliplatin, cisplatin, methotrexate, doxorubicin, bleomycin, etoposide, isoniazid, rifampin

also contribute to the resistance of proteins and nucleic acids to the alkylating effects of the corresponding toxicants [8]. However, the conjugation of phase I biotransformation products with glutathione can also result in the formation of metabolites with higher toxicity than their precursors.

THIRD PHASE OF XENOBIOTICS BIOTRANSFORMATION: MOLECULES-BIOTRANSPORTERS, THEIR FUNCTIONAL SPECIALIZATION

Currently, the third phase of biotransformation is particularly emphasized — the active secretion of xenobiotics and/or their metabolites into urine or bile, which is carried out by proteins belonging to the superfamily of secondary membrane-bound transporters MFS (Major Facilitator Superfamily) [6, 36] and the superfamily of ATP-binding cassette transporters (ABC transporters) [19]. The MFS includes solute carrier family (SLC) proteins (carriers) of the SLC22 [20] and SLC21 (OATP) [21], which carry out the transmembrane transport of “organic electrolytes” — structurally different compounds that have a negative, positive, or both charges (zwitterions) at physiological pH values. These include endogenous substrates of physiological significance, as well as pharmacologically and toxicologically significant xenobiotics [49, 51]. In addition to organic anion transporters (OAT), the SLC22 family includes organic cation transporters (OCT) and carnitine/zwitterion transporters (OCTN).

The ABC transporter superfamily currently comprises approximately 300 eukaryotic proteins that transport a wide variety of compounds [23]. These proteins use ATP energy to move various substrates across the cell membrane. Among ABC transporters, one can distinguish exporters, which transport toxins, drugs, and lipids out of the cell, and importers, which transport nutrients and other molecules into the intracellular space [19, 26, 35].

Phase III transporters are present in many tissues, including the liver, intestines, kidneys, and brain, where they form a barrier against the entry of xenobiotics into the body. These biomolecules play an important role in regulating the absorption, distribution, and excretion of many drugs and toxic xenobiotics, and are also involved in the efflux from cells of newly formed products of the second phase of biotransformation.

ORGANIC ANION TRANSPORTERS: STRUCTURE, TISSUE LOCALIZATION, AND MECHANISM OF TRANSPORT FUNCTIONS

Organic anion transporters play a significant role in the distribution and excretion of an exceptionally wide range of compounds, including endogenous metabolites (hormones, nutrients) and exogenous organic anions. Large hydrophobic organic anions, including a wide range of drugs, serve as OAT substrates. Transmembrane transport mediated by OAT occurs in numerous organs, including the kidneys, liver, brain, retina, adrenal glands, pancreas, intestines, and placenta [55].

The localization, substrate specificity, and ligands of the main OATs are presented in Table 5.

All members of the OAT family are characterized by a similar structure, a high level of genetic sequence conservation, and transport a wide range of weakly acidic drugs, such as loop and thiazide diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors, beta-lactam antibiotics, sulfonamides, and antivirals.

The OAT polypeptide chain, consisting of 536–556 amino acid residues, penetrates the cell membrane 12 times and forms a pore. Characteristic of this protein is the intracellular localization of the N- and C-terminal regions of the molecule and two large connecting loops between helices 1–2 and helices 6–7. Two domains containing ATP binding sites are located in the intracellular space of the cell.

The primary function of OAT is to transport one organic anion into the cell in exchange for another organic anion out of the cell. Although most OATs are Na-independent anion exchangers [49], their function is indirectly linked to the Na+ gradient through tertiary active transport, which involves Na,K-ATPase and Na-dependent dicarboxylic acid transport [53]. The uptake of organic anions into the cell occurs in exchange for intracellular α-ketoglutarate, which is a metabolite of the Krebs cycle and the preferred physiological counterion exiting the cell. Na-dependent α-ketoglutarate transport is maintained by the Na+ gradient created by Na,K-ATPase.

With broad substrate specificity, OATs can interact with a wide variety of compounds and transport not only small amphiphilic organic anions and uncharged molecules, but also xenobiotics and their metabolites, which are ionized during metabolism.

OATs function in interaction with enzymes of the first and second phases of biotransformation, actively participating in the distribution and elimination of metabolites [58]. OAT-3 is better adapted to the transfer of glucuronidated and sulfated xenobiotics than unmodified

Table 5. Transporters of organic anions of the organic anion transporters (OAT) subfamily [48]

Таблица 5. Транспортеры органических анионов подсемейства транспортеров органических анионов (OAT) [48]

Транспортер / Transporter	Ген / Gene	Локализация / localization	Субстраты лекарственных средств / Substrates-therapeutic agents
OAT-1	*SLC22A6*	Почки, сосудистое сплетение мозга, плацента / Kidneys, choroid plexus of the brain, placenta	Антигипертензивные средства, тиазидные диуретики, статины, антибиотики, противовирусные средства, нестероидные противовоспалительные препараты, соединения ртути, низкомолекулярные ксенобиотики, антагонисты гистаминовых рецепторов / Antihypertensives, thiazide diuretics, statins, antibiotics, antivirals, nonsteroidal anti-inflammatory drugs, mercury compounds, low molecular weight xenobiotics, histamine receptor antagonists
OAT-2	*SLC22A7*	Печень, почки / Liver, kidneys	Антибиотики, диуретики, антагонисты гистаминовых рецепторов, противовирусные средства, нестероидные противовоспалительные препараты, противоопухолевые средства / Antibiotics, diuretics, histamine receptor antagonists, antiviral agents, nonsteroidal anti-inflammatory drugs, antineoplastic agents
OAT-3	*SLC22A8*	Почки, эндотелий гематоэнцефалического барьера, сосудистое сплетение мозга, сетчатка глаза, семенники / Kidneys, endothelium of the blood-brain barrier, choroid plexus of the brain, retina, testes	Диуретики, антибиотики, противовирусные средства, антагонисты гистаминовых рецепторов, нестероидные противовоспалительные средства, низкомолекулярные ксенобиотики / Diuretics, antibiotics, antivirals, histamine receptor antagonists, nonsteroidal anti-inflammatory drugs, low molecular weight xenobiotics
OAT-4	*SLC22A11*	Почки, плацента, надпочечники / Kidneys, placenta, adrenal glands	Диуретики, антибиотики, нестероидные противовоспалительные препараты / Diuretics, antibiotics, nonsteroidal anti-inflammatory drugs
OAT-6	*SLC22A20*	Назальная слизистая, семенники, печень / Nasal mucosa, testes, liver	Эстрона сульфат, одоранты / Estrone sulfate, odorants
OAT-7	*SLC22A9*	Печень / Liver	Эстрона сульфат, дегидроэпиандростерона сульфат / Estrone sulfate, dehydroepiandrosterone sulfate
OAT-10	*SLC22A13*	Почки, мозг, сердце, тонкий и толстый кишечник / Kidneys, brain, heart, small and large intestines	Никотин, ураты / Nicotine, urates

organic anions [48]. Thus, the interaction between OATs and enzymes of the first and second phases of biotransformation is aimed at the inactivation of xenobiotics, the immunotoxicity of which may increase during their metabolism. This interaction also ensures the maintenance of homeostasis in terms of the formation and inactivation of signaling molecules involved in long-distance communication between various tissues and organs.

POLYPEPTIDE TRANSPORTERS OF ORGANIC ANIONS: STRUCTURE, TISSUE LOCALIZATION, AND MECHANISM OF TRANSPORT FUNCTIONS

Organic anion transporting polypeptides (OATPs) are members of the Na-independent transport system that transport numerous endogenous and exogenous amphiphilic organic anions with molecular masses greater than 350 Da across plasma membranes at physiological pH values [50]. These transporters transport bilirubin and various drugs (e.g., angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins, antihistamines, and antitumor agents) [39]. In addition, they are key players in the redistribution and elimination of various xenobiotics, including immunotoxicants, from cells [52].

OATPs contain 643–722 amino acids. Depending on the degree of glycosylation, the molecular mass varies from 65 to 120 kDa [38]. The transport channel is formed by a polypeptide chain that spans the cytoplasmic membrane 12 times and has six extracellular loops [56]. Glycosylation occurs actively on loops 2 and 5, where carbohydrate attachment sites are located [59]. Within the site, a pore-like space generates a positive charge due to the exposure of positively charged amino acids to the interior, resulting in the binding and transport of negatively charged molecules, which represent the bulk of OATP substrates, into the cell.

OATP is expressed in various epithelial cells (Table 6) [37]. In humans, OATP is divided into six families (OATP1–OATP6), which are further grouped into subfamilies based on the location of the gene encoding the protein. The mechanism of transport of various molecules by OATP has not yet been fully elucidated [37]. It is known that many OATPs are antiporters, i.e., they simultaneously transport anions across the membrane in opposite directions. In the proposed models,

Table 6. Human organic anion transporter proteins (OATP) [39]
Таблица 6. Белки-транспортеры органических анионов (OATP) человека [39]

Семейство / Family	Подсемейство / Subfamily	Локализация / localization	Переносимые субстраты / Transferable substrates
OATP-1	OATP1A2	Мозг, почки, печень, легкие, семенники, плацента / Brain, kidneys, liver, lungs, testes, placenta	Холаты, органические анионы / Cholates, organic anions
	OATP1B1	Печень / Liver	Холаты, билирубин / Cholates, bilirubin
	OATP1B3	Печень, злокачественные опухоли / Liver, malignant tumors	Холаты, билирубин, глутатион, простагландины, лейкотриены, трийодтиронин, тироксин / Cholates, bilirubin, glutathione, prostaglandins, leukotrienes, triiodothyronine, thyroxine
	OATP1C1	Глиальные клетки гипоталамуса, сосудистые сплетения гематоэнцефалического барьера, клетки Лейдига / Hypothalamic glial cells, choroid plexuses of the blood- brain barrier, Leydig cells	Холаты, трийодтиронин, тироксин, эстрон-3-сульфат / Cholates, triiodothyronine, thyroxine, estrone-3-sulfate
OATP-2	OATP2A1	Во всех тканях / In numerous tissues	Простагландины, тромбоксан / Prostaglandins, thromboxane
	OATP2B1	тРНК найдена во многих органах / tRNA is found in many organs	Бромсульфафталеин / bromosulfophthalein
OATP-3	OATP3A1	Во всех тканях / In numerous tissues	Эстрон-3-сульфат, простагландины / Estrone-3-sulfate, prostaglandins
OATP-4	OATP4A1	Во всех тканях / In numerous tissues	Таурохолат, трийодтиронин / taurocholate, triiodothyronine
	OATP4C1	Локализация неизвестна / Unknown localization	Трийодтиронин / triiodothyronine
OATP-5	OATP5A1	Эпителий протоков молочной железы / Epithelium of the mammary gland ducts	Нет данных / No data
OATP-6	OATP6A1	Семенники, мозг, плацента / Testicles, brain, placenta	Нет данных / No data

the largest pore diameter is observed on the cytoplasmic side. Conformational changes in the transporter molecule can cause the pore to open toward the extracellular space. Intracellular ions can act as energy sources for transporting other anions into the cell. It is assumed that one of these intracellular substrates is reduced glutathione (GSH), which can act as an energy donor when OATPs perform their functions of transporting substances into the cell [43]. The intracellular concentration of GSH, which is 1000 times higher than its content outside the cell, and its negative charge at physiological pH values can provide energy to OATP1 when performing its transport functions [27]. Moreover, it is the intracellular level of GSH, and not its transmembrane gradient, that plays a decisive role in implementing the OATP transport function [44].

OATPs play an active role in the functioning of the xenobiotic biotransformation system. Due to their expression in most tissues, OATPs play a major role in the transport of many endo- and exogenous compounds into virtually all cell types and associated tissues and organs [52].

A number of drug-drug interactions (DDIs) discovered in recent years have demonstrated the impossibility of explaining the biotransformation of drugs solely by the activity of phase I and phase II enzymes of xenobiotic metabolism. It has been shown that the interaction between cytochromes P450 (CYP) and transporters plays a key role in these processes [60], which can be mediated through altered metabolic pathways due to simultaneous changes in enzyme and transporter activity. Drugs targeting phase I and phase II enzymes can often be substrates or inhibitors of transporters. When using OATP inhibitors, plasma drug concentrations may increase and the risk of developing side effects such as hepatotoxicity, nephrotoxicity, and immunotoxicity may increase [47]. When both inhibitors are used concomitantly, the CYP-OATP interaction may result in a synergistic rather than additive effect. This interaction may be determined through co-regulation of protein expression. The expression of both components is believed to be regulated by a family of transcription factors known as nuclear receptors, such as PXR (pregnane X receptor), CAR (constitutive androstane receptor), FXR (farnesoid X receptor), and LXR (liver X receptor).

ORGANIC CATION TRANSPORT PROTEINS (OCAT) AND CARNITINE/ZWITTERION TRANSPORT PROTEINS (OCTN): STRUCTURE, TISSUE LOCALIZATION, AND MECHANISM OF TRANSPORT FUNCTIONS

Organic cation transporters (OCT) and carnitine/zwitterion transporters (OCTN) participate in the transport of organic cations across the cell membrane exclusively in the direction of their electrochemical gradient. Their molecular diversity is significantly lower than that of other transporters: three organic cation transporters are known — OCT1, OCT2, OCT3 — and three carnitine/zwitterion transporters — OCTN1, OCTN2, OCT6 [49, 61].

OCT and OCTN are present in many tissues, which indicates their active participation in tissue and organ metabolism (Table 7). They are particularly abundant in the liver, kidneys, brain, and intestines, where they participate in the absorption, distribution, and excretion of xenobiotics and endogenous metabolites. In the proximal renal tubules, OCT transporters are involved in the active secretion of hydrophilic endogenous and exogenous compounds into the urine.

They are structurally similar to other proteins of the MFS superfamily and consist of 543–557 amino acids forming 12 transmembrane helices (domains). Three N-glycosylation sites are located on a large extracellular loop between the first and second transmembrane domains, ensuring accurate folding and positioning in the cell membrane [29]. Phosphorylation sites are located on a large intracellular loop connecting the 6th and 7th helices. Protein kinases A (PKA), C (PKC), G (PKG) and calcium/calmodulin-dependent protein kinase II (CaMII) are involved in phosphorylation reactions [31]. The N- and C-terminal halves of the transporter form a cleft, and binding to ligands and substrate transport presumably occurs through interaction with amino acid residues facing the interior of the cleft [22].

The main substrates of these transporters are organic compounds of endogenous and exogenous origin, structurally unrelated to each other and carrying a positive charge at physiological pH. For transmembrane transport of organic cations, transporters use the negative charge existing on the inner surface of cell membranes [40]. Passive diffusion of cations occurs along the electrochemical gradient, causing the corresponding substrates to accumulate inside the cell in concentrations significantly higher (up to 10 times) than outside [32]. The higher the degree of ionisation of the substrates, the higher their affinity for the transporter and the rate of their transport as the pH decreases [28].

ATP-BINDING CASSETTE TRANSPORTERS OF THE ABC FAMILY: STRUCTURE, TISSUE LOCALISATION, MECHANISM OF TRANSPORT FUNCTIONS

ATP-binding cassette transporters (ABC) are the largest class of membrane-bound proteins that transport metabolic products across both the plasma membrane and the intracellular membranes of various

Table 7. Tissue distribution and substrate specificity of OCT/OCTN transporters [41]

Таблица 7. Тканевое распределение и субстратная специфичность транспортеров OCT/OCTN [41]

Транспортер / Transporter	Тканевое распределение / Tissue distribution	Основные эндогенные субстраты / Main endogenous substrates	Основные экзогенные субстраты / Main exogenous substrates
OCT-1	Печень, почки, тонкая кишка, легкие, скелетная мускулатура, головной мозг, жировая ткань, иммунные клетки / Liver, small intestine, kidney, lung, skeletal muscle, brain, adipose tissue, immune cells	Путресцин, гистидил-пролил-дикетопиперазин, салсолинол, агматин / Putrescine, hys-pro-diketopiperazine, salsolinol, agmatine	Метформин, ацикловир, пентамидин, фурамидин, оксиплатин, афлатоксин B1, этидиумбромид и др. / Metformin, acyclovir, pentamidine, furamidine, oxaliplatin, aflatoxin B1, ethidiumbromide, etc.
OCT-2	Почки, тонкая кишка, легкие, плацента, тимус, головной мозг, клетки внутреннего уха / Kidney, small intestine, lung, placenta, thymus, brain, inner ear cells	Ацетилхолин, дофамин, эпинефрин, норэпинефрин, серотонин, гистамин, путресцин, холин, салсолинол / Acetylcholine, dopamine, epinephrine, norepinephrine, serotonin, histamine, putrescine, choline, salsolinol	Амантидин, цисплатин, афлатоксин B1, этидиумбромид, паракват и др. / Amantadine, cisplatin, aflatoxin B1, ethidiumbromide, paraquat, etc.
OCT-3	Сердце, скелетная мускулатура, головной мозг, тонкая кишка, печень, легкие, почки, мочевой пузырь, молочная железа, кровеносные сосуды кожи / Heart, skeletal muscle, brain, small intestine, liver, lung, kidney, urinary bladder, mammary gland, skin blood vessels	Эпинефрин, норэпинефрин, гистамин, агматин, гистидил-пролил-дикетопиперазин, салсолинол / Epinephrine, norepinephrine, histamine, agmatine, cyclo(His-Pro), salsolinol	Лидокаин, метформин, оксиплатин, квинидин, этилэфрин и др. / Lidocaine, metformin, oxaliplatin, quinidine, etilefrine, etc.
OCTN-1	Почки, кишечник, брыжейка, сердце, скелетная мускулатура, головной мозг, молочная железа, тимус, простата, семенники, глаз, сперма, иммунные клетки / Kidney, intestine, mesentery, heart, skeletal muscle, brain, mammary gland, thymus, prostate, testis, eye, sperm, immune cells	Ацетилхолин, эрготионеин, глицил-бетаин, L-карнитин / acetylcholine, ergothioneine, glycinebetaine, L-carnitine	Квинидин, верапамил, ипратропиум, митоксантрон, доксорубицин, бетоницин и др. / Quinidine, verapamil, ipratropium, mitoxantrone, doxorubicine, betonicine, etc.
OCTN-2	Скелетная мускулатура, почки, простата, легкие, печень, поджелудочная железа, сердце, тонкая кишка, надпочечники, щитовидная железа / Skeletal muscle, kidney, prostate, lung, pancreas, heart, small intestine, adrenal gland, thyroid gland, liver	L-карнитин, холин / L-carnitine, choline	Милдронат, цефалоридин, эметин, верапамил, шпиронолактон, оксиплатин и др. / Mildronate, cephaloridine, emetine, verapamil, spironolactone, oxaliplatin, etc.
OCT-6	Семенники (клетки Сертоли и семенного протока), почки, лейкоциты, костный мозг / Testis (Sertoli cells and epididymal duct cells), kidney, leukocytes, bone marrow	L-карнитин, спермидин / L-carnitine, spermidine	Доксорубицин, блеомицин A5 / Doxorubicin, bleomycin A5

organelles: the endoplasmic reticulum, peroxisomes, and mitochondria [33]. These proteins are named for their use of ATP as an energy source to transport various molecules. It has been found that ABC transporters are involved in many pathological processes: in the development of multiple drug resistance, oncogenesis, autoimmune reactions, and degenerative protein metabolism pathology [19, 25].

ABC transporters differ in amino acid sequence, structural and domain structure and are divided into 7 subfamilies: ABCA, ABCB, ABCC, ABCD, ABCE, ABCF and ABCG. All ABC transporters can also be divided into complete transporters, which have four domains (2 transmembrane domains (TMD1, TMD2) and 2 nucleotide-binding domains (NBD1, NBD2)) and incomplete transporters, which have one TMD and one NBD in their structure [3, 26]. Incomplete transporters are located in the intracellular membranes of organelles and usually assemble into hetero- or homodimers. TMDs penetrate the membrane and have ligand binding sites on their intracellular side. NBD domains, located in the cytoplasm, have binding sites for two ATP molecules and possess ATPase activity. The energy of ATP hydrolysis is used to transport the substrate [45].

ABC transporters are located in virtually all tissues of internal organs, as well as in tumour cells. The most important for the transport of drugs, xenobiotics, including immunotropic substances, are representatives of the ABCB, ABCC and ABCG subfamilies

Table 8. Tissue distribution and substrate specificity of human ABC transporters [54]

Таблица 8. Тканевое распределение и субстратная специфичность ABC-транспортеры человека [54]

Транспортер / Transporter	Тканевое распределение / Tissue distribution	Основные субстраты / Main substrates
ABCB1 (Pgp)	Гематоэнцефалический барьер, печень, кишечник, почки, плацента, стволовые клетки / Blood-brain barrier, liver, intestine, kidney, placenta, stem cells	Противоопухолевые препараты (доксорубицин, винбластин, этопозид, паклитаксел, метотрексат), анальгетики (морфин), ингибиторы протеазы ВИЧ (ампренавир, индинавир), цитокины (IL-2, IL-4), антидиарейные препараты (лоперамид), антигельминтики (ивермектин, абамектин), противорвотные препараты (домперидон, ондасетрон), сердечные гликозиды (дигоксин), антидепрессанты (амитриптилин, пароксетин), антибиотики (эритромицин, тетрациклины), средства против подагры (колхицин, гистамин), антагонисты H_2-рецептора (циметидин), блокаторы кальциевых каналов (верапамил), противоэпилептические препараты (карбамазепин, ламотригин, фенобарбитал, габапентин) / Anticancer drugs (doxorubicine, vinblastine, etoposide, paclitaxel, methotrexate), analgesics (morphine), HIV protease inhibitors (amprenavir, indinavir), cytokinese (IL-2, IL-4), antidiarrheal agents (loperamide), anthelminthic agents (ivermectin, abamectin), antiemetics (domperidone, ondansetron), cardiac glycosides (digoxin), antidepressants (amitryptiline, paroxetine), antibiotics (erythromycin, tetracyclines), anti-gout agents (colchicines, histamine), H_2-receptor antagonists (cimetidine), calcium channel blocker (verapamil), antiepileptic drugs (carbamazepine, lamotrigine, phenobarbital, gabapentin)
ABCC1 (MRP1)	Легкие, семенники, почки, скелетная и сердечная мускулатура, плацента / Lung, testes, kidney, skeletal and cardiac muscle, placenta	Противоопухолевые препараты: этопозид, тенипозид, винкристин, лейкотриены C4 (LTC4), D4, E4, различные глутатион-, глюкуронид- и сульфат-конъюгаты, а также неконъюгированные соединения (флуоресцеин) / Anticancer drugs: etoposide, teniposide, vincristine, leukotriene C4 (LTC4), D4, E4, various glutathione, glucuronide, and sulfate conjugates, but also unconjugated compounds (fluorescein)
ABCC2 (MRP2)	Гематоэнцефалический барьер, печень, кишечник, почки, плацента, легкие / Blood-brain barrier, liver, intestine, kidney, placenta, lung	Противоопухолевые препараты: этопозид, тенипозид, винкристин, лейкотриены C4 (LTC4), D4, E4, различные глутатион-, глюкуронид- и сульфат-конъюгаты, а также неконъюгированные соединения (флуоресцеин) / Anticancer drugs: etoposide, teniposide, vincristine, leukotriene C4 (LTC4), D4, E4, various glutathione, glucuronide, and sulfate conjugates, but also unconjugated compounds (fluorescein)
ABCC3 (MRP3)	Надпочечники, кишечник, поджелудочная железа, желчный пузырь, плацента, печень, почки, простата / Adrenal gland, intestine, pancreas, gallbladder, placenta, liver, kidney, prostate	Транспортер органических анионов со значительным сходством субстратной специфики с MRP1 и MRP2 / Organic anion transporter with considerable overlap in drug substrates with MRP1 and MRP2
ABCC4 (MRP4)	Яичники, семенники, почки, легкие, простата / Ovary, testes, kidney, lung, prostate	Противоопухолевые препараты, такие как метотрексат, 6-меркаптопурин, тиогуанин / Anticancer drugs such as methotrexate, 6-mercaptopurine, thioguanine
ABCC5 (MRP5)	Печень, семенники, скелетная и сердечная мускулатура, мозг / Liver, testes, skeletal and cardiac muscle, brain	BQ-123 (анионный циклопентапептид, антагонист рецептора эндотелина) / BQ-123 (an anionic cyclopentapeptide and endothelin receptor antagonist)
ABCG2/BCRP	Гематоэнцефалический барьер, плацента, печень, кишечник, молочная железа, стволовые клетки / Blood-brain barrier, placenta, liver, intestine, breast, stem cells	Противоопухолевые препараты, значительное субстратное перекрывание с Pgp, MRP1 и MRP2, антрациклины, митоксантрон, бисантрен, празолин / Several anticancer drugs; considerable substrate overlap with Pgp, MRP1, and MRP2, anthracyclines, mitoxantrone, bisantrene, prazolin

(Table 8). In addition to the drugs themselves, these proteins transport their sulphated, glutathionylated and glucuronidated metabolites. The most studied representative of the ABC family in humans is the ABCB1 transporter (P-glycoprotein, Pgp, MDR1). This transporter is highly expressed in cells of the blood-brain barrier, liver, intestine, kidneys, placenta, and stem cells [19].

P-glycoprotein works as a transmembrane pump that removes drugs and other xenobiotics from cells, increasing the excretion of drugs or toxins in bile and urine. The apical (or luminal) location of P-glycoprotein

in the epithelium of the intestinal mucosa leads to a decrease in drug absorption from the gastrointestinal tract. When the functioning of this mechanism of transport of xenobiotic metabolites, which is provided by P-glycoprotein, is disrupted under conditions of severe oxidative stress, other metabolite elimination systems become inadequate or insufficient. These metabolites begin to accumulate in tissue structures, where they exert their toxic effects.

The development of multidrug resistance (MDR) is associated with high activity of the ABCC2 transporter, which is involved in the transport of conjugated drugs and toxins into bile and urine [42]. By removing anticancer drugs from cells and reducing their intracellular concentration, ABC transporters play a key role in the development of tumour MDR, which negatively affects the effectiveness of chemotherapy.

Breast cancer resistance protein (BCRP, ABCG2) is a semi-transporter and functions as a homodimer, actively removing anthracyclines, DNA topoisomerase I inhibitors, and tyrosine kinases from tumour cells [46].

CONCLUSION

Phase II biotransformation reactions are traditionally regarded as detoxification processes. However, there are examples of chemical compounds that, in second-phase metabolism reactions, are converted into active electrophilic metabolites capable of covalent interactions with macromolecules in the body, including proteins, by binding to nucleophilic sites of these macromolecules. As a result of such interactions, reactive metabolites modify the antigenic specificity of these macromolecules as autoantigens and induce autosensitisation of the body, which can contribute to the development of allergic and autoimmune diseases, as well as increase the procarcinogenic activity of chemical carcinogens.

Phase III metabolism transporters are an integral part of the xenobiotic biotransformation system and play an important role in its functioning through close interaction with phase I and II enzymes. This role consists not only in the conversion of various types of endogenous metabolites, drugs and toxins, but also in the implementation of the interconnection between metabolic processes and signal transmission. The importance of studying transporter proteins is particularly relevant at present, as it is linked to the development of methods and approaches for evaluating the effectiveness and consequences of the use of newly created drugs.

ADDITIONAL INFORMATION

Author contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

Funding. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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