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ALTERATION IN LIPID COMPOSITION OF PLASMA MEMBRANES OF SENSITIVE AND RESISTANT GUERIN CARCINOMA CELLS DUE TO THE ACTION OF FREE AND LIPOSOMAL FORM OF CISPLATIN

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***Aim*: To study *in vivo* changes of lipid composition of plasma membranes of sensitive and resistant to cisplatin Guerin carcinoma cells under influence of free and liposomal cisplatin forms. *Materials and Methods*: The isolation of plasma membranes from parental (sensitive) and resistant to cisplatin Guerin carcinoma cells was by differential ultracentrifugation in sucrose density gradient. Lipids were detected by method of thin-layer chromatography. *Results*: It was determined that more effective action of cisplatin liposomal form on resistant cells is associated with essential abnormalities of conformation of plasma membrane due to change of lipid components and architectonics of rafts. It results in the increase of membrane fluidity. *Conclusion*: Reconstructions in lipid composition of plasma membranes of cisplatin-resistant Guerin carcinoma cells provide more intensive delivery of drug into the cells, increase of its concentration and more effective interaction with cellular structural elements.**
***Key Words:* tumor, plasma membranes, lipids, drug resistance, cisplatin liposomal form.**

It is known that cytostatic's interaction with plasma membrane is the first stage of realization of cytotoxic effect of antitumor drugs. At the same time it is determined that change of membrane structure, as well as direct and reverse transport of these drugs through it, is one of the main mechanisms of drug resistance [1–3].

There are many reports that plasma membranes of tumor cells differ from membranes of cells without signs of malignant transformation by conformation and increased content of cholesterol, glycosphingolipids, sphingomyelin and phospholipase D [4]. Special attention at that is drawn by changes of content of cholesterol and its ethers, inasmuch quantity of these components influences structural-functional state of membranes and their fluidity [5–8]. Experiments *in vitro* have demonstrated that increase of cholesterol causes increase of rigidity of plasma membrane of cells of endothelium and human K562 erythroleukemia cells. It is supposed that above mentioned effects are conditioned by reconstructions of actinic cytoskeleton that is activated by destruction of lipid rafts, which are rich in cholesterol. In system *in vivo* was proved that decrease of cholesterol in blood plasma by means of inhibition of its synthesis by simvastatin [9] has caused decrease of its content in lipid rafts of plasma membrane of tumor cells. At the same time it was showed that the diet can alter the cholesterol content both in blood plasma of animals as well as lipid rafts of plasma membrane of tumor cells [10, 11].

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Abbreviations used: CL – cholesterol; CP – cisplatin; FCP – free form of cisplatin; LCP – liposomal form of cisplatin; LPO – lipid peroxidation; PC – phosphatidylcholine; PE – phosphatidylethanolamine; PGC – parental (sensitive) Guerin carcinoma; RGC – resistant Guerin carcinoma; PL – phospholipids; PS – phosphatidylserine; PUFAs – polyunsaturated fatty acids; SM – sphingomielyn.

At the same time there is no much information about correlation between lipids in plasma membranes and their functional role in development and overcoming of drug resistance. Besides, clinical observations of the last years argue about encouraging prospects for overcoming of malignant tumor resistance [12, 13] with the help of liposomal drug forms of cytostatics. However, mechanisms of their positive effect are not completely clear. Taking this into consideration, we have set ourselves to define changes of content and ratio of total lipids and phospholipids of plasma membranes in cells of sensitive and resistant Guerin carcinoma in consequence of action of cisplatin (CP) and its liposomal form.

MATERIALS AND METHODS

Two groups of animals (Wistar rats-male) were involved in the research: with the resistant and sensitive to CP Guerin carcinoma. These tumor strains were obtained from National Bank of Cell Lines and Transplanted Tumors of R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology, National Academy of Sciences of Ukraine (Kyiv, Ukraine).

The keeping of animals, all stages of experimental researches, including euthanasia, met the conventional international requirements of humane treatment with laboratory animals, and regulations approved by bioethics commission of the R.E. Kavetsky IEPOR of NAS of Ukraine. The animals with sensitive (PGC) and CP-resistant (RGC) tumors were divided into three groups: FCP-rats received a free form of CP; LCP-rats received a liposomal form of CP; control animals received (i/p) saline.

The isolation of plasma membranes from the tumor cells of rats was carried out by the method of differential ultracentrifugation in sucrose density gradient. Concentration of protein in suspension of plasma membranes was determined by Lowry method. The purity of mem-

brane specimens was controlled by the activity of marker enzymes Na^+,K^+-ATPase and 5'- nucleotidases.

Qualitative and quantitative content of total lipids and phospholipids was determined with the micromethod of thin-layer chromatography using plates "Sorbfil" TLC-A ("Imid Ltd", Krasnodar, Russia). For this purpose with the help of compound of solvents chloroform : methanol 1 : 1 from Guerin carcinoma cells the lipids were extracted. Thin-layer chromatography of total lipids was carried out only in one direction in system of solvents hexane : diethyl ether : glacial acetic acid 85 : 15 : 1. The thin-layer chromatography of phospholipids was carried out in two mutually perpendicular directions. As first system of solvents was used chloroform : methanol : benzol : ammonia 65 : 30 : 10 : 6, second — chloroform : methanol : benzol : acetone : glacial acetic acid : water 70 : 30 : 10 : 5 : 4 : 1. After evaporation of solvents the plates were processed by 10% H_2SO_4 in methanol and were heated 5 min. at 180 °C. The obtained chromatograms were scanned, for processing of images was applied PictureJ program. The content of lipids was expressed in percentage (%).

Total lipids in membranes of parental (sensitive) and resistant to CP Guerin carcinoma cells the content of phospholipids, cholesterol, di- and triglycerides and ethers of cholesterol has been determined. In addition, the following individual phospholipids were evaluated: lysophosphatidylcholine, sphingomyelin, phosphatidylserine, phosphatidylinositol, phosphatidylcholine, phosphatidylethanolamine.

The statistic processing of obtained results was conducted with the help of Student's *t*-criterion.

RESULTS AND DISCUSSION

In the first stage of the research the evaluation of total lipids composition in membranes of sensitive and resistant to CP Guerin carcinoma was conducted (Table 1).

It has been determined that under the effect of free cisplatin (FCP) in group of animals with sensitive Guerin carcinoma the indexes of total phospholipids of cell membranes have not been changed significantly, but action of cisplatin liposomal form (LCP) causes the increase of phospholipids, decrease of di- and triglycerides and ethers of cholesterol. Increase of phospholipids by action of LCP in composition of total lipids of plasma membrane takes place as the result of decrease of content of diglycerides of 34%, triglycerides of 24% and ethers of cholesterol of 31%, i.e., main lipid components of low density lipoproteins. More significant abnormalities (probable or with peculiar tendencies) were obtained by analysis of content of total lipids in membranes of resistant to cisplatin Guerin carcinoma. The wide range of determined changes in content of total lipids in resistant tumors and absence of them in membranes of sensitive tumors let us state that by the development of resistance, tumor cells acquire such features, which differ them from parental, and these differences are well observed by comparison of groups of control: decrease of content of phospholipids, increase of cholesterol, reduction of diglycerides part, decrease of triglycerides, increase of ethers of cholesterol.

On the basis of the results of own studies we state that key link in chain of tumor cells resistance development mechanism is increase of cholesterol and its ethers in membranes, inasmuch as value of these indexes in membranes of resistant Guerin carcinoma cells increased 22 and 81%, respectively, compared with the similar in sensitive Guerin carcinoma, and it is the evidence of increase of their rigidity. Under the influence of FCP these indexes changed a little, but when using liposomal drug form we were observing some differences. First of all, they concerned changes of cholesterol and its ethers in membranes of cells of resistant tumors and revealed itself by decrease of their content 16 and 57%, respectively, compared with control, and therefore by increase of fluidity.

The obtained data fit with modern ideas of the role of cholesterol in support of structural homeostasis of cell membranes. Free cholesterol is obligatory structural component of cell membrane. Today cholesterol is regarded as the most important regulator of liquid lipid bilayer of membrane [14, 15]. It stabilizes the membrane, interacting by its hydroxyl group with polar heads of phospholipids and sphingolipids. Free cholesterol belongs to surface zone of phospholipid monolayer and is an integral part of this monolayer: molecules of cholesterol are located between hydrophobic ends of phospholipid molecules. In this very zone takes place the lipid-protein interaction.

The analysis of the results of the reseach second stage on distribution of phospholipids, which are the main components of cell membranes and provide their physicochemical properties, semipermeability for low-molecular compounds, activity of membrane-binding enzymes, course of reactions of signal transduction cascade [16], has demonstrated that in cell membranes of animals with sensitive and resistant to CP Guerin carcinoma no significant changes of components content of this group lipids (lysophosphatidylcholine, sphingomyelin, phosphatidylinositol and phosphatidylcholine) under the effect of different drugs forms were observed (Table 2).

When determining the content of phosphatidylserine in group of animals with resistant to CP Guerin carcinoma some tendency to its decrease in response to the use of liposomal form of drug was observed. According to the data of researches, the main functions of phosphatidylserine are regulation of membrane proteins and transport of different compounds inside cell and excretion from the latter the decay products [17].

More significant data were obtained concerning indexes of kephaline (phosphatidylethanolamine). It is known that content of phosphatidylethanolamine constitutes 20–40% of total pool of phospholipids of mammals cell membranes and mainly localizes on the inner leaflet of plasma membrane [18, 19]. Phosphatidylethanolamine is considered to move on the outer leaflet of plasma membrane in zone of cell division in process of cell cytokinesis [20]. Functional

role of this component of phospholipids pool is not completely clear. There is evidence that phosphatidylethanolamine acts as molecular chaperone, to be exact, assists the renovation of ordinary tertiary structure of damaged protein, transition of primary structure of polypeptides in unique tertiary. There is still no final answer to the question of its influence on the lipid homeostasis.

According to the own data, in membranes of resistant Guerin carcinoma cells, in which were not administered drugs of platinum, the quantity of kephaline was 25% less compared with the similar index of parental tumor. The following dynamics of changes of this index under the influence of antitumor drugs was determined. In parental carcinoma was observed decrease of quantity of phosphatidylethanolamine both under the influence of FCP and LCP.

The obtained data suggest that LCP, due to lipid component, is able to modify membrane owing to redistribution of its lipid composition, and it has positive effect on the use of this cytostatic.

For the correct interpretation of obtained data they should be analyzed in aspect of functional role of studied lipids in structure of plasma membrane. According to the conventional fluid-mosaic model, the basis of membrane is formed by bimolecular layer of lipids (lipid bilayer), which in any membrane serves two main functions: it acts as barrier for ions and molecules, and acts as matrix for functioning of receptors and enzymes. Lipid bilayers are formed by amphiphilic molecule of phospholipids in phase aqueuse. These molecules are called amphiphilic, because they consist of two parts, which are different by their water solubility: polar head, which has high closeness to water, i.e., hydrophilic, and tail, which is formed by nonpolar carbohydrate links of fatty acids. This part of molecule has low closeness to water, i.e., hydrophobias. Fluidity (microviscosity) of lipid bilayer is determined by quantity of polyunsaturated fatty acids: the more fatty acids, the higher fluidity.

The components of bilayer are phosphatidylcholine and phosphatidylethanolamine, which localize on the outer and inner sides of membrane correspondently. Phosphatidylcholine contains significantly more unsaturated acids, than phosphatidylethanolamine; therefore ratio of these phospholipids may in certain way characterize total nonsaturation of lipid bilayer. Among minor phospholipids the sphingomyelin mainly localizes in inner bilayer and has carbohydrate links of saturated fatty acids, and phosphatidylserine localizes in inner side and has mainly polyunsaturated fatty-acid remains [21–23].

On the assumption of these ideas the influence of studied drugs on the nonsaturation of lipid bilayer of plasma membrane of cells of sensitive and resistant to CP Guerin carcinoma has been analyzed. First of all, should be mentioned that unsaturation of surface part of lipid bilayer is determined by correlation of two main components: sphingomyelin, which contains remains of only saturated fatty acids, and phosphatidylcholine, which has one saturated and one unsaturated acid. According to such notions, own studies have defined that this particle of lipid bilayer of plasma membrane of parental tumor cells (at that animals were not getting cytostatics) is "more fluid" compared with the similar one in membranes of resistant tumor cells (Table 3). The value of mentioned index turned out to be 25% higher than in plasma membranes of resistant form of tumor. The particle of lipid bilayer, which involves fatty-acid remains of lipids of both monolayers, localizes deeper. It is characterized in the ratio of total content of phosphatidylcholine and sphingomyelin to the total content of phosphatidylethanolamine and phosphatidylserine and distinguishes itself by greater

Table 1. The indexes of distribution of total lipids in membranes of sensitive and resistant Guerin carcinoma cells depending on the form of drug

Tumor's sensitivity	Drug form	Phospholipids, %	Cholesterol, %	Diglycerides, %	Triglycerides, %	Ethers of cholesterol, %
PGC	FCP	35.2 ± 2.0	37.2 ± 1.6	10.6 ± 0.8	7.9 ± 0.6	8.8 ± 0.9
	LCP	43.2 ± 1.4(↑)*	35.9 ± 2.2	8.0 ± 0.8(↓)*	6.8 ± 0.7(↓)*	6.2 ± 1.1(↓)*
	Control	34.6 ± 2.1	35.3 ± 2.2	12.1 ± 1.4	9.0 ± 1.6	9.0 ± 1.2
RGC	FCP	36.9 ± 1.8(↑)*	41.6 ± 1.9	7.1 ± 0.5	6.3 ± 0.2	8.2 ± 1.5(↓)*
	LCP	42.8 ± 1.4(↑)*	36.1 ± 1.2(↓)*	7.5 ± 0.35	6.7 ± 0.6	7.0 ± 0.6(↓)*
	Control	25.7 ± 1.7(↓)**	43.0 ± 1.3(↑)**	8.1 ± 0.58(↓)**	7.1 ± 0.8(↓)**	16.3 ± 1.3(↑)**

Note: significant alteration of indexes ($p<0.05$): * compared with control; **compared with content of the similar constituents in sensitive Guerin carcinoma; n = 10.

Table 2. Indexes of distribution of tumor cells membrane individual phospholipids with different sensitivity to cisplatin depending on the form of drug

Tumor's sensitivity	Drug form	Lysophosphatidylcholine, %	Sphingomyelin, %	Phosphatidylserine, %	Phosphatidylinositol, %	Phosphatidylcholine, %	Phosphatidylethanolamine, %
PGC	FCP	12.3 ± 1.2	10.7 ± 0.8	8.1 ± 0.2 (↓)*	10.1 ± 1.4	37.7 ± 1.0 (↑)*	19.3 ± 0.6 (↓)*
	LCP	14.1 ± 0.5 (↑)*	10.1 ± 0.6	8.0 ± 0.4 (↓)*	12.7 ± 0.4	37.2 ± 2.1 (↑)*	19.0 ± 0.5 (↓)*
	Control	10.1 ± 0.8	10.5 ± 0.4	15.2 ± 0.1	11.6 ± 0.8	29.1 ± 1.7	23.5 ± 0.9
RGC	FCP	14.2 ± 0.6 (↑)*	10.2 ± 0.5	8.4 ± 0.6 (↓)*	10.9 ± 0.6	35.8 ± 1.0 (↑)*	18.9 ± 0.9
	LCP	14.3 ± 0.4 (↑)*	10.0 ± 0.5	7.8 ± 0.3 (↓)*	11.2 ± 0.4	37.4 ± 1.5 (↑)*	21.2 ± 0.9 (↑)***
	Control	10.2 ± 0.2	13.6 ± 0.8	15.1 ± 0.5	12.3 ± 1.8	30.2 ± 1.7	17.7 ± 1.0 (↓)**

Note: significant alteration of indexes ($p<0.05$): * compared with control; **compared with sensitive Guerin carcinoma; ***compared with the similar constituent in sensitive Guerin carcinoma; n = 10.

Table 3. Evaluation of unsaturation of plasma membranes lipid bilayer

Type of tumor	Sensitive Guerin carcinoma			Resistant Guerin carcinoma		
Group of animals/index	SM/PC	PC + SM/ PE + PS	CL/PL	SM/PC	PC + SM/ PE + PS	CL/PL
Control	0.36 ± 0.02	1.02 ± 0.04	1.02 ± 0.03	0.45 ± 0.03	1.34 ± 0.04	1.67 ± 0.04
FCP	0.28 ± 0.03	1.76 ± 0.03*	1.05 ± 0.04	0.28 ± 0.03*	1.68 ± 0.04**	1.12 ± 0.03*
LCP	0.27 ± 0.02*	1.41 ± 0.03*	0.83 ± 0.02*	0.27 ± 0.02*	1.63 ± 0.03*	0.84 ± 0.03*

Note: significant alteration of indexes ($p<0.05$): * compared with control; n = 10.

increase (31%) of correlation of lipid components in plasma membranes of resistant Guerin carcinoma cells (see Table 3).

Administration of FCP causes decrease in ratio of sphingomyelin to phosphatidylcholine in phospholipids of membranes of sensitive and resistant Guerin carcinoma 22 and 38%, respectively, compared with control. The similar tendency was observed also under the influence of LCP. Decrease of correlation between sphingomyelin and phosphatidylcholine in phospholipids of membranes of parental and resistant Guerin carcinoma takes place 25 and 40%, respectively, though numerical expression of index of this correlation in both cases had the same value (0.27).

The evaluation of influence of antitumor drugs on total unsaturation of lipid bilayer, which is characterized by correlation of total content of phosphatidylcholine and sphingomielyn to phosphatidylethanolamine and phosphatidylserine, has showed inverse tendency of changes. Administration of FCP causes increase of these indexes, decreasing unsaturation of lipid bilayer of membranes of both types of tumor 73 and 25%, respectively, compared with control. LCP also decreases unsaturation of lipid bilayer of membranes of both types of tumor, but less, 38 and 22%, respectively.

Thus, under the influence of both forms of CP the rigidity of membrane in area of fatty-acid links of total lipid bilayer of plasma membranes of tumor cells increases. Though both drugs cause monodirectional changes, FCP causes 1.7 times increase of rigidity of plasma membrane of parental Guerin carcinoma compared with resistant, while by use of LCP this index increases 1.2 times only. Decrease of content of phospholipids, which contain polyunsaturated carbohydrate remains of fatty acids, may be conditioned by oxidative stress and lipid peroxidation (LPO), which develop in process of cytotoxic effect of CP [24, 25]. The consequence of this is decrease of pool of phospholipids, which contain polyunsaturated fatty acids. By administration of LCP in cell are found additional lipids, which may be used both for renewal of pool of phospholipids and for providence of needs of cell in energy [26].

It is necessary to mention that in contrast to FCP, which arrives in cell directly from blood plasma through ion canals, LCP may arrive in cell at least by three ways. Liposomes with CP may be absorbed by cell through mechanism of endocytosis; they also may directly interact with plasma membranes of tumor cells (lipid component of liposome embeds in membrane of cell) and indirectly, with the help of macrophages, which catch LCP by phagocytosis and deliver CP, which has released, to the tumor [27–29].

According to the data of own studies, by administration of LCP to the animals with parental Guerin carcinoma (see Table 1) in composition of total lipids of plasma membranes of tumor cells the total content of phospholipids increases compared with animals, to which was administered FCP, and control — 23 and 25%, respectively. It should be mentioned that introduction of FCP to the animals with sensitive Guerin carcinoma doesn't change correlation in composition of total lipids of tumor cells plasma membranes, but increases content of phospholipids compared with control.

According to the data of researches increase of quantity of the main structural phospholipids — phosphatidylcholine and phosphatidylethanolamine (PC and PE) is accompanied with intensification of cholesterol biosynthesis. However, at that is observed increase in ratio of cholesterol and phospholipids (CL/PL) that influences the fluidity of monolayer. It is confirmation of the fact that cholesterol is regulator of fluidity of membranes [30]. It is known that two times increase of its concentration in membrane compared with phospholipids converts bilayer from liquid state in gel [18, 21, 23]. By that membrane loses ability to rebuild and serve its functions. The mentioned data are the evidence that coefficient CL/PL is general indicator of fluidity of membrane. The direct correlation between change of fluidity of tumor cell membranes and their penetrability for CP has been determined [31, 32].

According to own researches, in membranes of resistant form of Guerin carcinoma the index of CL/PL is 64% higher, than in cells of parental form of tumor (see Table 3), that is an evidence of decrease of present monolayer fluidity. PGC does not change mentioned index in plasma membranes of parental Guerin carcinoma, while in membranes of cells of resistant tumors decreases it of 33%, increasing this way fluidity of membranes. LCP decreases this index in both forms of tumor 19 and 50%, respectively. So, LCP decreases rigidity of membrane lipid bilayer of resistant tumor cells to the level of sensitive form of Guerin carcinoma, renewing its functional activity. It sets conditions for support of optimal activity of membrane-related enzymes and provision of transport through membrane.

It also should be taken into account that plasma membrane is heterogeneous by its structure — smooth areas of lipid bilayer are changed into areas, in which big amount of protein molecules are located. These are particular areas, where fluidity of lipid bilayer is regulated by proteins, which lie on the surface of bilayer or are immersed in it, but are fixed by given area of membrane with the help of electrostatic forces or microfilaments of cytoskeleton (peripheral proteins), as well as integral proteins, which penetrate bilayer. Around these protein molecules arise specific regions — domains, which contain certain content of lipids and usually possess higher rigidity. Two types of microdomains of lipid bilayer were determined, which in researches were called lipid rafts. They serve as peculiar fundament for protein molecule, which covalently are linked with molecules of lipids. The numerous researches have showed that these areas play important role in administration by cell of its functions [30, 33–38].

Rafts, which contain caveolin, attract special attention. This is integral protein, which, binding cholesterol and lipid bilayer, forms on the surface of cells the rafts in the form of holes — caveolae. Caveolae serve in cell following functions: transport of different substances

through membrane and transduction of different signals [39, 40]. So, rafts provide compartmentalization of receptors of cells and determine directions of processes of signal transduction. Dynamics of rafts and their changes are one of the key links in realization of signal cascades with participation of cytoskeleton [41, 42]. Series of data are the evidence that association with rafts may be governing factor, which determines activity of integral membrane proteins [43, 44].

The experimental studies have showed that lipids of liposomal form of CP are embedding in surface layer of plasma membrane, or the modification of lipid rafts and protein receptors takes place [45, 46].

Concerning the analysis of the results of own researches from these positions, it was already mentioned that in tumor cell plasma membrane of resistant Guerin carcinoma the content of free cholesterol and its ethers increases compared with parental form 22 and 81%, respectively (Table 1). At that, the part of cholesterol ethers, which are the obligatory structural components of lipid rafts, significantly increases. It should be mentioned that according to the data of [47] the development of resistance to CP is accompanied with expression of transport proteins, in which functioning the lipid rafts and cholesterol are involved. The role of changes of cholesterol content in membrane in functioning of lipid rafts was showed [48, 49].

The results of own researches also have showed that ratio of ethers of cholesterol and free cholesterol in plasma membrane of tumor cells of resistant form constitutes 0.38, while in membranes of parental form only 0.25. It is the evidence of higher levels of transition of cholesterol molecules through membrane. The officinal form of CP is almost not influencing the content of free cholesterol and its ethers in plasma membrane of sensitive Guerin carcinoma, while LCP decreases content of cholesterol ethers on 31% and doesn't influence the content of free cholesterol. Thereupon may be assumed that LCP does not change structure of rafts essentially, but causes the decrease of metabolism of cholesterol in membrane. The ratio of cholesterol ethers and free cholesterol in plasma membrane of tumor cells of animals, which were influenced by LCP, constitutes 0.17, that is 1.5 times less compared with the similar ratio in plasma membrane of parental tumor cells and in animals, which were not administered antitumor drug. It is the evidence that the level of transference of cholesterol molecules through membrane is lower.

By action of FCP on the resistant form of Guerin carcinoma in plasma membranes the content of free cholesterol decreases insignificantly (3.3%), but the content of cholesterol ethers decreases essentially (50%). The ratio of cholesterol ethers to free cholesterol in plasma membrane of these tumor cells constitutes 0.20 that is 1,9 times less compared with control. In contrast to FCP, liposomal drug form decreases content of both free cholesterol (16%) and ethers of cholesterol — 57%. The mentioned changes of both components of cell membranes are the evidence that LCP damages both the structure of rafts and metabolism of cholesterol in plasma membrane of resistant Guerin carcinoma cells. Taking into account the results of own researches and other data, the administration of cisplatin liposomal form to the animals with resistant Guerin carcinoma has caused damage of balance in system of regulation by cholesterol and its ethers of plasma membrane fluidity. The fact of essential decrease of content of free cholesterol and ethers of cholesterol in consequence of LCP action, by our opinion, may be connected with change of integrity and quantity of lipid rafts of plasma membrane by interaction with liposomes.

The results of our research give ground to state that LCP, in contrast to FCP, together with decrease of cholesterol content and products of its metabolism in plasma membrane of Guerin carcinoma cells is able to call the conformation reconstructions of lipid rafts and, in consequence of this, to change its fluidity.

So, the obtained pooled data are: displacement of quantitative correlation of lipid compounds and alteration of architectonics of rafts that causes increase of fluidity of plasma membranes, allows to assume that one of the mechanisms of more effective action of LCP compared with FCP on the cells both of sensitive and resistant Guerin carcinoma, are structural-functional changes in plasma membrane. The determined reconstructions in a lipid composition of plasma membranes of resistant tumors provide more intensive entrance of drug into cells, increase of its concentration and more effective interaction with intracellular structures.

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