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Liver-targeted delivery of nucleic acid by liposomes modified with a glycoconjugate

Olesya O. Koloskova,*[a,b] Anastasia S. Nosova,[a,b] Inga S. Shchelik,[b] Igor P. Shilovskiy,[a] Yurii L. Sebyakin[b] and Musa R. Khaitov[a]

[a] *State Scientific Center 'Institute of Immunology', 115478 Moscow, Russian Federation. Fax: +7 499 612 8929; e-mail: oo.koloskova@nrcii.ru*

[b] *Institute of Fine Chemical Technologies, Moscow Technological University, 119571 Moscow, Russian Federation. Fax: +7 495 936 8901; e-mail: c-221@yandex.ru*

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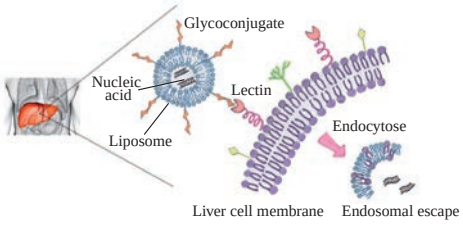
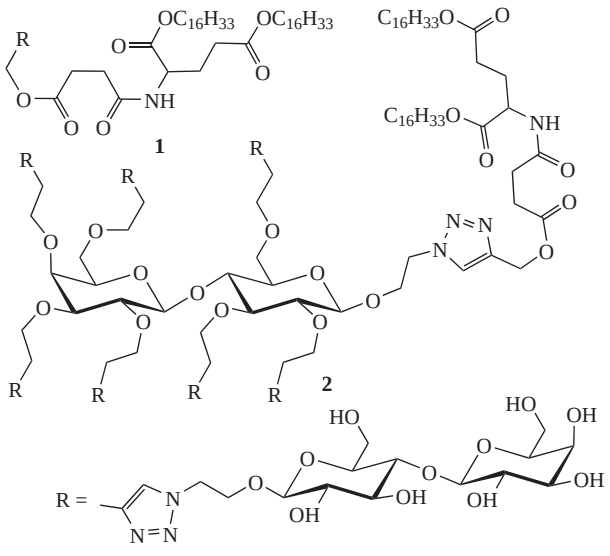
A drug delivery system based on liposomes has been modified by targeted vectors based on a glycoconjugate, and the vector structure has been optimized. The glycoconjugate in liposomes almost fourfold increases the transfection efficiency of the delivery system in specific human liver cell line (HepG2) in comparison with that of unmodified lipopeptide-based liposomes.



Selective drug delivery directly into a target organ can significantly reduce side effects on other cells and organs and maximize the therapeutic effect of the drug.[1,2] Cell surface receptors are good candidates for selective drug delivery. Therefore, the use of ligands that specifically bind to the receptors of target organ cells is a promising approach.[3–5] It is well known that liver cells have a high level of lectin expression, and lectins are capable of binding the terminal residues of D-galactose. Such specific proteins are named asialoglycoprotein receptors and galectins.[6,7] The modification of nanoparticle surfaces by oligosaccharides and their derivatives promotes their targeting.[8–11]

Lipid-based nanoparticles are the most effective and non-toxic drug delivery systems due to their good biocompatibility and biodegradability and a wide range of opportunities for the modification of specific properties.[12–15] Liposomes based on OrnOrnGlu(C_{16})$_2$ were chosen previously as the most effective nucleic acid delivery system.[16] In this work, we modified liposomes by neutral carbohydrates Lac(C_{16})$_2$ **1** and (Lac)$_7$Lac(C_{16})$_2$ **2** with terminal lactose derivatives. A high binding efficiency with the galactose-binding lectin *Ricinus communis* (RCA1) was demonstrated for such glycoconjugates.[17]



Carbohydrate derivatives with 10 wt% of lipid composition were added during the formation of a thin lipid film. The transfection efficacy was measured using a luciferase test[16] on a model of the non-specific cell line HEK293T and the specific human liver cell line HepG2 (Table 1).

It was shown that glycoconjugates in liposomes led to an almost fourfold increase in the transfection efficiency on HepG2 cell line as compared with that of unmodified liposomes based on lipopeptide, while there was a decrease in the transfection efficiency of plasmid pGL3 by liposomes with carbohydrate derivatives on the non-specific cell line HEK293T (data not shown). This fact is very important in anti-hepatitis C drug design.

In addition, it was found that a branched lactose derivative reduced the transfection efficacy of liposome in comparison with that of a mono-carbohydrate derivative. This effect is due to the shielding of a liposomal surface by carbohydrate residues from interaction with nucleic acid and reduction of its compaction. The branched lactose derivative is characterized by a cluster effect,[18,19] while its absence can be explained by the fact that a carbohydrate component is directly bonded to the hydrophobic component in glycoconjugates, and the monosaccharide groups are at a level of the polar heads of amphiphiles in liposomes.

Table 1 Luciferase gene expression in HepG2 cells transfected by lipoplexes with 0.2 μg of pGL3 plasmid coding luciferase gene (N = 5).

Liposome composition	Luciferase gene expression on a control basis (%)	
	HEK293T cells	HepG2 cells
OrnOrnGlu(C_{16})$_2$	100	100
OrnOrnGlu(C_{16})$_2$ + Lac(C_{16})$_2$	70 ± 30	410 ± 30
OrnOrnGlu(C_{16})$_2$ + (Lac)$_7$Lac(C_{16})$_2$	50 ± 25	150 ± 20
pGL3	0.1 ± 1	0.1 ± 1

Table 2 IC_{50} on HE293T cells for different liposome compositions.

Liposome composition	IC_{50}/μg ml^{-1}
OrnOrnGlu(C_{16})$_2$	347.6 ± 38.3
OrnOrnGlu(C_{16})$_2$ + Lac(C_{16})$_2$	351.6 ± 39.9
OrnOrnGlu(C_{16})$_2$ + (Lac)$_7$Lac(C_{16})$_2$	353.2 ± 42.6

This location leads to difficulties in the specific interaction between a lectin active center and a glycosyl determinant. Nevertheless, glycoconjugates in a lipoplex increase the transfection efficiency on the specific human liver cells HepG2, adding a necessary targeting function to liposomes. The transfection activity of the delivery system with Lac(C_{16})$_2$ increases fourfold in comparison with that of unmodified liposomes.

An MTT test was conducted to compare the toxicity of glycoconjugate-modified and unmodified liposomes. Lactose derivatives in liposomes did not lead to an increase in the cytotoxicity (Table 2).

The obtained data evidence the prospects of the developed delivery system based on liposomes with the carbohydrate vector as a targeted carrier to specific human liver cells (HepG2). This fact is promising for the development of methodologies toward the design of anti-hepatitis C drugs.

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References

1 Z. Fang, L.-Y. Wan, L.-Y. Chu, Y.-Q. Zhang and J.-F. Wu, *Expert Opin. Drug Deliv.*, 2015, **12**, 1943.
2 M. M. Zacche, S. Srikrishna and L. Cardozo, *Res. Reports Urol.*, 2015, **7**, 169.
3 G. A. Duncan and M. A. Bevan, *Nanoscale*, 2015, **7**, 15332.
4 I. S. Shchelik, A. I. Magasumova and Yu. L. Sebyakin, *Makrogeterotsikly*/*Macroheterocycles*, 2015, **8** (2), 199.
5 A. I. Magasumova, E. D. Shuina, Yu. L. Sebyakin, U. A. Budanova and I. S. Shchelik, *Tonkie Khim. Tekhnologii.*, 2015, **10** (4), 22 (in Russian).
6 J.-J. Yan, J.-Z. Liao, J.-S. Lin and X.-X. He, *Tumor Biol.*, 2015, **36**, 55.
7 M. T. Haynes and L. Huang, *Drug Deliv. Transl. Res.*, 2014, **4**, 61.
8 N. Jain, V. Rajoriya, P. K. Jain and A. K. Jain, *J. Nanopart. Res.*, 2014, **16**, 2136.
9 Z. Shen, W. Wei, H. Tanaka, K. Kohama, G. Ma, T. Dobashi, Y. Maki, H. Wang, J. Bi and S. Dai, *Pharmacol. Res.*, 2011, **64**, 410.
10 U. Westerlind, J. Westman, E. Törnquist, C. I. Smith, S. Oscarson, M. Lahmann and T. Norberg, *Glycoconjugate J.*, 2004, **21**, 227.
11 M. S. Wadhwa and K. G. Rice, *J. Drug Target.*, 2003, **11**, 255.
12 L. Ya. Zakharova, R. R. Kashapov, T. N. Pashirova, A. B. Mirgorodskaya and O. G. Sinyashin, *Mendeleev Commun.*, 2016, **26**, 457.
13 A. M. Sumina, O. O. Koloskova, G. A. Sarychev, U. A. Budanova and Y. L. Sebyakin, *Russ. J. Biopharm.*, 2013, **5** (4), 35.
14 A. S. Abu Lila and T. Ishida, *Biol. Pharm. Bull.*, 2017, **40**, 1.
15 Q. Lin, J. Chen, Z. Zhang and G. Zheng, *Nanomedicine*, 2014, **9**, 105.
16 O. O. Koloskova, A. A. Nikonova, U. A. Budanova, I. P. Shilovskiy, I. A. Kofiadi, A. V. Ivanov, O. A. Smirnova, V. V. Zverev, Y. L. Sebyakin, S. M. Andreev and M. R. Khaitov, *Eur. J. Pharm. Biopharm.*, 2016, **102**, 159.
17 U. A. Budanova, I. S. Shchelik, O. O. Koloskova and Yu. L. Sebyakin, *Mendeleev Commun.*, 2016, **26**, 205.
18 R. T. Lee and Y. C. Lee, *Glycoconjugate J.*, 2000, **17**, 543.
19 M. Taichi, S. Kitazume, K. K. H. Vong, R. Imamaki, A. Kurbangalieva, N. Taniguchi and K. Tanaka, *Glycoconjugate J.*, 2015, **32**, 497.

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