The influence of SARS-CoV-2 receptor binding domain on the model lipid membrane structure: a SANS study

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Introduction

Detailed information about the structure and properties of lipid membranes is essential for building reliable models describing response of living cell to different environmental perturbations, of both physical and chemical origin [1]. Dynamics of interaction of living cell with a viral agent (with SARS-CoV-2 being one of the latest well-known examples) can not be reduced to only considering the binding receptors dynamics, because the structure and properties of the membrane itself, if influenced by the viral agent, can modulate a number of biophysical processes and therefore affect the penetration of the agent.

In this contribution we discuss our recent results obtained by small-angle neutron scattering (SANS) in multi-component liquid systems, containing both model membranes (DMPC lipid vesicles), cholesterol and melatonin adducts in various concentrations and SARS-CoV-2 receptor binding domain (RBD, Fig. 1) - a part of the viral spike, which is responsible for its biding with cells receptors.

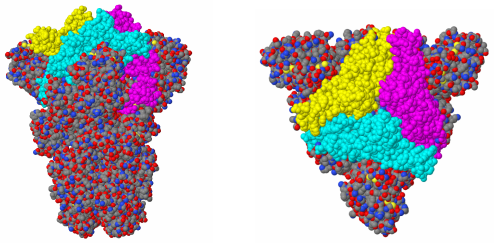

Fig. 1. Spatial structure of three subunits of SARS-CoV-2 spike glycoprotein (PDB code 6ZB4 [2], front view on the left and top view on the right). Receptor binding domain (RBD) in each of the three chains is shown in different color

Results

A number of systems containing the model cell membranes in form of vesicles (Fig. 2) built from 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC) molecules have been prepared (see *Materials and Methods* for more details) and investigated experimentally with SANS (Fig. 4) and vibrational spectroscopy (Fig. 5), both infrared and Raman. Experimental studies were supplemented by computer simulations using classical molecular dynamics (MD) methods (Fig. 3).

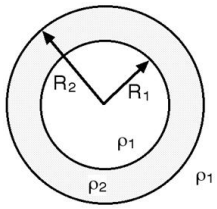

Fig. 2. Definitions of structural (R_1, R_2) and scattering (ρ_1, ρ_2) parameters to the vesicle components

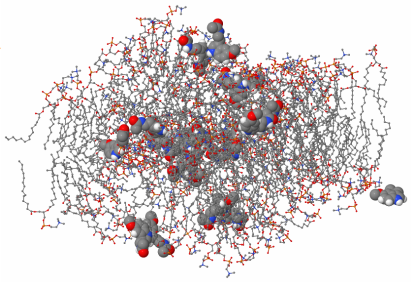

Fig. 3. Location of melatonin molecules within the model lipid membrane (according to MD simulations)

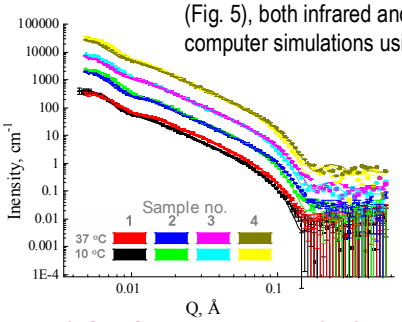

Fig. 4. SANS spectra and their fits for the studied systems: 1 – pure DMPC vesicles in water, 2 – DMPC+15mol.% of cholesterol, 3 – DMPC+30mol.% of cholesterol, 4 – DMPC+30mol.% of cholesterol + RBD of SARS-CoV-2

Table 1. Geometrical properties of DMPC lipid vesicles, modeling cell membranes, in liquid system depending on its composition; see Fig. 2 for the parameter definitions.

System	Temperature, °C	Inner radius of vesicle, Å	Thickness of lipid bilayer, Å
DMPC + 30% cholesterol in D_2O	10	235	44,6 ± 0,1
	37	239	43,6 ± 0,1
DMPC + 30% cholesterol + RBD SARS-CoV-2 in D_2O	10	250	44,6 ± 0,1
	37	233	41,7 ± 0,1
DMPC + 30% melatonin in D_2O	10	230	39,6 ± 0,1
	37	252	35,8 ± 0,1
DMPC + 30% melatonin + RBD SARS-CoV-2 in D_2O	10	230	39,3 ± 0,1
	37	259	35,6 ± 0,1

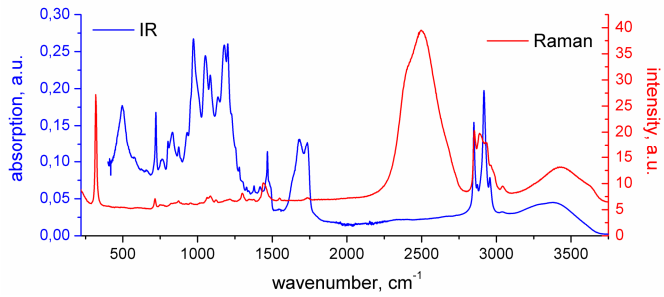

Fig. 5. Vibrational spectra (IR and Raman) of DMPC lipid vesicles in presence of 30% cholesterol and SARS-CoV-2 receptor binding domain

Conclusion

Obtained data quantify structural properties of the model lipid membranes thereby providing a direct way to test the existence of mutual interactions of RBD and the membrane. The influence of cholesterol on the key structural characteristics of the studied systems has been found to be in a good agreement with that observed in other similar lipid systems [4,5].

Materials and Methods

SANS spectra were measured for heavy water (D_2O)-based liquid systems containing: DMPC; DMPC + 15 mol.% of melatonin; DMPC + 30 mol.% of melatonin; DMPC + 30 mol.% of melatonin + RBD of SARS-CoV-2; DMPC + 15 mol.% of cholesterol; DMPC + 30 mol.% of cholesterol; DMPC + 30 mol.% of cholesterol+ RBD of SARS-CoV-2. The measurements were performed at temperatures of 10 °C and 37 °C. SAS software used for preliminary processing of the obtained data is described in more details in [3].

Molecular dynamics simulations were performed in GROMACS package (version 2020) using united-atom GROMOS 54a7 force field.

References

[1] L.A.Bulavin, A.E. Mikhailov, P.K.Kuzmiche, V.V. Chupin, V.I. Borshchevskiy, I.V. Chizhov, D.V. Soloviov // *Ukr. J. Phys.*- 2020.- Vol. 65(9).- pp. 778-778.
[2] C.Toelzer, K. Gupta, S.K.N. Yadav, U. Borucu, A.D. Davidson, M.Kavanagh Williamson, D.K. Shoemark, F.Garzoni, O.Staufer, R. Milligan, J. Capin, A.J. Mulholland, J.Spatz, D.Fitzgerald, I.Berger, C.Schaffitzel // *Science.* – 2020. - Vol. 370 (6517). - pp. 725-730.
[3] A.G.Soloviev, T.M. Solovjeva, O.I. Ivankov, D.V. Soloviov, A.V. Rogachev, A.I. Kuklin // *J. Phys. Conf. Series.* - 2017. – Vol. 848(1). – 012020.
[4] T. Murugova, O. Ivankov, E. Ermakova, T. Kondela, Hrubovčák, Pavol, V. Skoi, A. Kuklin, N. Kučerka // *Gen. Physiol. Biophys.* – 2020. – Vol. 39(02). - pp. 135-144.
[5] T. Kondela, E. Dushanov, M. Vorobyeva, K. Mamatkulov, E. Drolle, D. Soloviov, P. Hrubovčák, K. Kholmurodov, G. Arzumanyan, Z. Leonenko, N. Kučerka // *Biochim. Biophys. Acta (BBA) – Biomembranes.* - 2021. – Vol. 1863(9). – 183651.

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