DESCRIPTION FOR THE GENERAL PUBLIC

Amphotericin B (AmB) belongs to a group of antibiotics widely used in the treatment of the systemic mycotic infections. The mechanism of action of this antibiotic is based on the formation of an oligomeric pore structure within the fungal plasma membrane (PM) by interaction with membrane ergosterol. Despite that AmB binds preferentially to ergosterol, it can also bind to cholesterol in the mammalian PM including human cells and cause severe cellular toxicity, what often compromises a successful treatment of patients. The lipids and sterols content and their lateral organization at the cell PM appear to be significant for the AmB binding. However, the mechanisms by which cells control in space and time lateral organization of lipids in the PM remain unclear. It is known that in human cells several ATP binding cassette (ABC) transporters (including ABCA1) play a crucial role in lipid translocation, the PM organization, cholesterol redistribution and efflux. In this project we aim at explaining, how the activity of ABC transporters modifies the PM organization and therefore impacts the binding and toxicity of AmB in human cells.

Our research project is based on interdisciplinary approaches that combine cellular and molecular biology as well as biochemistry with novel biophysical techniques. Our preliminary data show that human cell lines possessing a functional ABCA1 transporter in their plasma membrane are more resistant to the AmB. We would like to confirm and extend these results by using human cell lines stable or transiently expressing functional and non-functional ABCA1 transporter. The cells will be challenged with AmB and its derivatives, and the cell growth, morphology and viability will be monitored. Next, using different biophysical techniques we will verify how AmB localizes within the PM bilayer and how this localization is affected by the activity of ABCA1.

Up to date, there is no clear experimental data showing a link between the plasma membrane lateral organization, the activity of ABC transporters, and AmB binding and toxicity in living cells. We would like to focus on this research problem and investigate whether ABC transporters, involved in lipids and sterols transport, might influence the binding and toxicity of AmB. This knowledge is important for general understanding of plasma membrane organization and could be helpful in designing novel modified AmB molecules. It is thus substantial in the development of non-toxic therapies of systemic mycoses, whose number grow, especially in immunosuppressed patients, and as a response to more and more widely used treatments with broad-spectrum antibacterial antibiotics. Moreover, the research on plasma membrane and its lateral organization are of great interest of the scientific community. The basic cellular processes depend on extracellular signals that are transmitted *via* cell surface receptors, and the PM lateral organization plays a central role in this process. The results would therefore help in revealing these mechanisms.