DESCRIPTION FOR THE GENERAL PUBLIC

Tumorigenesis is strictly correlated with mutations and deregulation of gene expression and protein function leading to abnormal and non-physiological behaving of the cells inside the organism. Throughout the years of research on cancer, it has been shown that expression, regulation and function of numerous plasma membrane (PM) and PM-associated proteins are altered during tumor progression. Examples of such proteins are: the epidermal growth factor receptor (EGFR) and metalloproteinases (MMPs). Recent studies have shown that in tumor cells, cholesterol content is higher compared to normal cells, suggesting a direct link between tumor development and the PM cholesterol level. As ABCA1, a member of the ATP binding cassette (ABC) transporters family, is important for cholesterol redistribution and efflux and may control the lateral organization of the PM. Depending of the type of cancer, it has been shown that ABCA1 play either a pro- or anti- tumorigenesis role. However, in melanoma cancer no direct link between ABCA1 activity and tumor development has been seen. Nevertheless, some studies evidenced that high cholesterol level within melanoma cells is linked to tumor proliferation and invasion. The aim of this project is to determine the role of ABCA1 activity in disruption of the raft-related organization of a few proteins implied in carcinogenesis potentially leading to an alteration of melanoma development and propagation.
Our research project is based on multidisciplinary approaches covering cellular and molecular biology as well as biochemical and biophysical techniques. The first objective will be to assess distribution of proteins of interest within the PM of melanoma cells using microscopy as well as investigate how do they dynamically organize within the PM by using fluorescence lifetime imaging microscopy and a biophysical approaches based on fluorescence correlation spectroscopy. To confirm that ABCA1 is indeed driving the differential distribution and dynamic organization of investigated proteins, we will alter ABCA1 expression in the melanoma cells. Using the melanoma cell lines and clones with altered ABCA1 expression, we will then study the potential role of ABCA1 for melanoma development and propagation by studying the capacity of proliferation and growth of the cells, as well as cell migration and invasion ability. Finally, to further investigate the role of cholesterol in melanoma carcinogenesis we will use compounds that modulate the cholesterol level at the PM.

Up to date, several studies have shown the implication of ABCA1-mediated cholesterol redistribution in the development of different types of cancer. However, there are no direct evidences for a link between ABCA1 activity and melanoma, which is very aggressive and deadly because of the difficulty to detect it in an early stage and its poor prognosis once metastasis begin to form. Our project will focus on this area and investigate whether ABCA1 is able to disrupt carcinogenesis-associated molecular organization of protein-lipid domains within the PM of melanoma, thus leading to alteration of tumor development and propagation processes. Any information allowing us to identify the role of ABCA1 in the dynamic organization and activity of these proteins may help us to further understand the importance of the PM dynamic organization in cancers and thus potentially for designing new therapeutic approaches.