ABSTRACT

The ATP-Binding Cassette A1 (ABCA1) transporter is a key protein in cholesterol homeostasis in mammals. In connection to the reverse cholesterol transport pathway, several diseases such as Tangier Disease and atherosclerosis have been associated with defects of ABCA1 activity. Moreover, the transporter is also able to modulate the plasma membrane organization in mammalian cells, as well as the cholesterol content and distribution within the plasma membrane. This activity may influence the signalization and function of plasma membrane proteins or proteins interacting with components of the plasma membrane. Due to its high dynamic, the specific ABCA1-mediated modulation of plasma membrane-associated proteins in mammalian cells remains elusive. However, the development of new biophysical techniques offering high spatial and temporal resolution made more advanced investigations in this field possible.

In this study, using a combination of cellular biology approaches and state-of-the-art biophysical techniques, we first report that ABCA1-mediated cholesterol efflux was able to promote the resistance toward amphotericin B, a polyene antibiotic used for the treatment of systemic mycoses. The drug, which targets cholesterol within the mammalian plasma membrane, was forming bulk structures made of amphotericin B and cholesterol exported by ABCA1, which prevents the wide insertion of the antibiotic within the membrane and reduces subsequent toxicity.

Moreover, as cholesterol is accumulated in cancer cells, we wanted to investigate ABCA1-mediated modulation mechanism on cholesterol content within the plasma membrane of human melanoma. We demonstrated for the first time the impact of ABCA1 activity in human melanoma. We showed that the metastatic derived cell line Hs294T overexpressed ABCA1, which led to the modification of the plasma membrane lateral organization, lipid order and fluidity based on the redistribution of cellular cholesterol content within the membrane. This plasma membrane modulation enhanced extracellular matrix degradation as well as formation of active integrin clusters and mature focal adhesions, promoting metastatic processes such as migration and invasion.

Collectively, the data suggest that ABCA1 activity, by modifying the plasma membrane lateral organization and lipid order in mammalian cells, influences crucial biological processes that could promote cells resistance towards cholesterol targeting drug as well as human melanoma development.