SFB 35 Colloquia in Membrane Transport

Venue: Medical University Vienna, Center for Physiology and Pharmacology,

Institute of Pharmacology, Waehringerstrasse 13a, 1090 Vienna,

"**Leseraum**"

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"Uncovering clinically relevant mutations in membrane transporters by genetic analysis linked to the determination of erythrocyte membrane protein expression"

Balázs Sarkadi

The human red blood cell (RBC) membrane contains more than 300 integral membrane proteins, many with high relevance to disease conditions or pharmacological interventions. We have developed a flow cytometry method for the quantitative determination of the RBC membrane expression levels of selected membrane transporters, and examined their molecular genetic background, as well as their potential value in medical diagnostics as biomarkers.
One example presented in this talk is the ABCG2 xeno- and endobiotic transporter, modulating the absorption and metabolism of pharmacological agents and causing multidrug resistance in cancer. ABCG2 is also involved in uric acid elimination and its impaired function is causative in gout. Analysis of ABCG2 expression in the erythrocyte membranes of healthy volunteers and gout patients showed an enrichment of lower expression levels in the gout patients, correlating with a genetic polymorphism, causing a Q141K variant protein. In addition, based on RBC expression levels, we found stop and frameshift mutations, as well as a relatively frequent, novel ABCG2 mutation (ABCG2-M71V). This variant, according to cellular expression studies, causes reduced protein expression, although with preserved transporter capability. Molecular dynamics simulations indicated a stumbled dynamics of the mutant protein, while ABCG2-M71V expression in vitro could be corrected by therapeutically relevant small molecules, with a potential in allele-specific gout treatment.
Another example is the plasma membrane calcium pump (PMCA4b) of the RBC membrane, which showed heterogeneous RBC expression levels in healthy volunteers. By genetic analysis, we found a correlation of the low PMCA4b expression levels with a minor haplotype in the erythroid cell specific regulatory region of this protein. This minor haplotype, now characterized in detail, seems to be correlated with sensitivity to malaria infection.
These results suggest that personalized medicine should consider the genetic analysis linked to RBC membrane protein expression, and these studies may provide a new tool to uncover clinically important variants of membrane proteins.

CV Balázs Sarkadi

Balázs Sarkadi, MD, Ph.D., spent several years as a post-doc and then as a visiting scientist at major universities in the United States and Canada. He is research professor at Semmelweis University, member of the Hungarian Academy of Sciences, past president of FEBS, member of several international research societies including the Academia Europeae. His research has been focusing on membrane proteins, including the investigation of ABC membrane transporters, which play a major role in the multidrug resistance of cancer, in general pharmacology, and in stem cell function. He has published more than 280 papers in international scientific journals, with a citation number over 13,000 and a h-index of 60. He has several international patents already in commercial applications.

SUMMARY OF RESEARCH AND TEACHING ACTIVITY

I have been mostly working in biochemical and physiological research in Hungary, but spent several years as a post-doc and then as a visiting scientist at major universities and research centers in the United States and Canada. During the past 10 years, I was heading the Membrane Research Group as professor at Semmelweis University, while also working at the National Institute of Haematology, performing both research and diagnostic activities. In 2005 I became member of the Academia Europeae, in 2007 served as president of the Federation of European Biochemical Societies (FEBS), in 2010 became full member of the Hungarian Academy of Sciences. I am currently member of several international research societies, and vice president of the International Cell Research Organization (ICRO-UNESCO).
My research has been focusing on the investigation of ABC membrane transporters, which play a major role in the multidrug resistance of cancer, in general pharmacology, and in normal and cancer stem cell function. With my colleagues, we have devised new methods for the functional analysis of ABC transporter proteins, and developed compounds that modulate their function. My current work is still partly focusing on studying ABC membrane transporters and the complex regulation of protein expression and cellular signaling in stem cells, and recently I have initiated a project for membrane protein diagnostics. We have a current project focusing on the regulation of membrane transporters in normal and cancer stem cells, including the generation of induced pluripotent stem cells and directed tissue differentiation.

I have published more than 280 research papers in international scientific journals, with a citation number over 15,000 (Google Scholar), or over 12,200 (WoS), and an h-number of 65/60. In the past 10 years, my 91 publications received over 1650 citations (WoS). I am a Research Professor of Semmelweis University, Budapest, Hungary, actively participating in the education of graduate and postgraduate students. I served as a supervisor for 17 Ph.D. students, who already successfully obtained their doctoral degrees, while I currently supervise 3 Ph.D. students.