ATTILA AMBRUS

Semmelweis University
Faculty of Medicine
Department of Biochemistry

Address: Tűzoltó u. 37-47., H-1094 Budapest, Hungary

RESEARCH AREA

The mitochondrion is an organelle inside the cell that serves as a powerhouse. In case the mitochondrial energy-generating processes (delivered by specific enzymes) get compromised, due to e.g. a genetic mutation that affects a key enzyme, severe clinical symptoms may arise; the generally neurological, cardiological, and/or hepatological manifestations often lead to premature death. The group of enzymes that was selected for our investigations comprises the mitochondrial alpha-keto (or 2-oxo) acid dehydrogenase multienzyme complexes (OADHc), which serve multiple pivotal roles in the energy metabolism of the mitochondrion. In the future we wish to initiate the development of enzyme replacement strategies against relevant OADHc deficiencies, where the healthy forms of the enzymes are delivered directly into the mitochondrion to replace the impaired enzymes. We also wish to design small molecule drug candidates in the near future to control the generation of harmful reactive radicals by OADHc and counteract the compromised enzymatic efficacy. Another proposed intervention approach is to reinforce by adaptor drug molecules the at times loosened obligate attachments among enzyme components in the greater enzyme complexes. For all of these approaches to be successful, first we need to investigate the relevant molecular pathomechanisms and related structures, which is part of our research program. Selected research results will potentially be also applicable in the supplemental treatments of other neuronal disorders (like stroke, neurodegenerative disorders, etc.).

TECHNIQUES AVAILABLE IN THE LAB

Recombinant DNA techniques, protein expression and purification (chromatography), mass spectrometry, NMR and circular dichroism spectroscopy, X-ray crystallography, cryo-electron microscopy, enzyme kinetics, molecular dynamics simulation, drug candidate design, other biophysical and biochemical laboratory techniques.

SELECTED PUBLICATIONS

Nagy, B., Polak, M., Ozohanics, O., Zambo, Z., Szabo, E., Hubert, A., Jordan, F., Novaček, J., Adam-Vizi, V., **Ambrus, A.** (2021) Structure of the dihydrolipoamide succinyltransferase (E2) component of the human alpha-ketoglutarate dehydrogenase complex (hKGDHc) revealed by cryo-EM and cross-linking mass spectrometry: Implications for the overall hKGDHc structure. **Biochim Biophys Acta (General Subjects)1865(6):** 129889.

Szabo, E., Wilk, P., Nagy, B., Zambo, Z., Bui, D., Weichsel, A., Arjunan, P., Torocsik, B., Hubert, A., Furey, W., Montfort, W.R., Jordan, F., Weiss, M.S., Adam-Vizi, V., **Ambrus, A.** (2019) Underlying molecular alterations in human dihydrolipoamide dehydrogenase deficiency revealed by structural analyses of disease-causing enzyme variants. **Hum Mol Genet 28:** 3339-3354.

Szabo, E., Mizsei, R., Wilk, P., Zambo, Z., Torocsik, B., Weiss, M.S., Adam-Vizi, V., **Ambrus, A.** (2018) Crystal structures of the disease-causing D444V mutant and the relevant wild type human dihydrolipoamide dehydrogenase. **Free Radic Biol Med 124:** 214-220.

Ambrus, A., Adam-Vizi, V. (2018) Human dihydrolipoamide dehydrogenase (E3) deficiency: novel insights into the structural basis and molecular pathomechanism. **Neurochem Int 117:** 5-14.

Ambrus, A.[#], Wang, J.[#], Mizsei, R.[#], Zambo, Z., Torocsik, B., Jordan, F., Adam-Vizi, V. (2016) Structural alterations induced by ten disease-causing mutations of human dihydrolipoamide dehydrogenase analyzed by hydrogen/deuterium-exchange mass spectrometry: Implications for the structural basis of E3 deficiency. **Biochim Biophys. Acta (Molecular Basis of Disease) 1862:** 2098-2109. (#=contributed equally)