Universität Basel

Research Project

The role of the endoplasmic reticulum in the metabolism of xenobiotics

Third-party funded project

Project title The role of the endoplasmic reticulum in the metabolism of xenobiotics
Principal Investigator(s) Odermatt, Alex ;
Organisation / Research unit
Departement Pharmazeutische Wissenschaften / Molecular and Systems Toxicology (Odermatt)
Department
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The research module “The role of the endoplasmic reticulum in the metabolism of xenobiotics” is part of the ProDoc Education Module “Predictive Toxicology”.

The uptake, distribution, metabolism and excretion of nutrients and drugs are essentially regulated in the intestine, liver and kidneys by a coordinated action of receptors, transport proteins and metabolizing enzymes. This allows living organisms to cope with toxic chemicals taken up by food (adaptation to food availability and quality), metabolites of drugs, and toxic endogenous chemicals (hormone metabolites, oxidized fat). To improve the toxicity prediction, the function of the enzymes, receptors and transporters involved in detoxification reactions need to be understood in the context of the situation of these proteins inside a given cell. Thus, the exact intracellular localization of these proteins and the impact of the conditions in a specific compartment inside a cell need to be elucidated, and appropriate assay systems have to be developed for safety assessment of chemicals.ă

This research module addresses the role of the endoplasmic reticulum (ER) in the metabolism of exogenous and endogenous chemicals, and the role of altered ER function for the metabolism and toxicity of chemicals. The ER plays an important role in the detoxification of xenobiotics and endogenous metabolites. Therefore, elucidation of the consequences of impaired ER function for the metabolism and toxicity of xenobiotics is important regarding the development of safer drugs.

We propose to 1) identify and characterize transporters in the ER for drug metabolites, 2) study the impact of the membrane topology of microsomal epoxide hydroxylase and its allelic variants on substrate turnover/detoxification efficacy, and 3) identify xenobiotic metabolizing short-chain dehydrogenase/reductases in the ER and investigate the impact of impaired ER function on xenobiotics metabolism.

To achieve our goal, we will use a range of different *in vitro* assays, cell- and animal models to study the functions of transporters and enzymes in the ER and to assess the impact of altered ER function on the metabolism and toxicity of xenobiotics.

The proposed research is relevant for uncovering basic mechanisms of the metabolism of endogenous and exogenous compounds in health and disease states. The knowledge gained from the proposed research is relevant for safety considerations for drugs and industrial chemicals. The proposed projects provide a unique opportunity for the establishment of collaborations and provide a multidisciplinary training opportunity across multiple areas of the Predictive Toxicology program.

Keywords Endoplasmic reticulum, epoxide hydrolase, dehydrogenase, reductase, xenobiotic, transport, metabolism
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Add publication

Published results

1519894, Meyer, Arne; Strajhar, Petra; Murer, Céline; Da Cunha, Thierry; Odermatt, Alex, Species-specific differences in the inhibition of human and zebrafish 11β-hydroxysteroid dehydrogenase 2 by thiram and organotins, 0300-483X, Toxicology, Publication: JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

2237809, Meyer, Arne; Vuorinen, Anna; Zielinska, Agnieszka E; Strajhar, Petra; Lavery, Gareth G; Schuster, Daniela; Odermatt, Alex, Formation of threohydrobupropion from bupropion is dependent on 11β-hydroxysteroid dehydrogenase 1, 1521-009X, Drug metabolism and disposition, Publication: JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

2237812, Meyer, Arne; Vuorinen, Anna; Zielinska, Agnieszka E; Da Cunha, Thierry; Strajhar, Petra; Lavery, Gareth G; Schuster, Daniela; Odermatt, Alex, Carbonyl reduction of triadimefon by human and rodent 11β-hydroxysteroid dehydrogenase 1, 0006-2952, Biochemical pharmacology, Publication: JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

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Specify cooperation partners

ID	Kreditinhaber	Kooperationspartner	Institution	Laufzeit - von	Laufzeit - bis
99697	Odermatt, Alex	Arand, Michael, Co-applicant	Institut für Pharmakologie und Toxikologie, Universität Zürich	01.10.2009	31.12.2014