Universität Basel

Research Project

Cellular toxicity of xenobiotics

Third-party funded project

Project title Cellular toxicity of xenobiotics
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The research interests of the group of Stephan Krähenbühl are mainly clinical and mechanistic aspects of rare toxicities not primarily associated with the mode of action of a drug, the so called idiosyncratic toxicity. Due to these characteristics, this type of toxicity is usually not detected during the development phase and appears only after introduction of a drug or chemical on the market. Most drug withdrawals are due to this type of toxicity. Target organs are mostly the liver, but may also be skeletal muscle, nervous system, bone marrow or any other organ. Mechanisms associated with this type of toxicity are immunological (mostly T-cell driven) or non-immunological (so called metabolic) toxicity. Regarding the non-immunological type of idiosyncratic toxicity, many features can be reproduced in vitro using isolated cells, cell cultures and/or isolated cell organelles exposed to high concentrations of a drug or drug metabolites. This observation has led to the concept that patients showing this type of toxicity have risk factors rendering them more sensitive to drug effects than the average patient. Examples of such risk factors include for instance alcohol consumption for hepatotoxicity associated with paracetamol or certain mitochondrial diseases for hepatotoxicity associated with valproate. Our research in this field had therefore principally three aims: 1. to dissect mechanisms of this type of toxicity in vitro (cell cultures, isolated cell or cell organelles) and in vivo in animals, and 2. to find out possible risk factors compatible with the mechanism, and 3. to find out biomarkers reflecting this type of toxicity. We have already successfully used Laser Scanning Microscopy for the demonstration that a newly developed antibody against OCTN2 (a high affinity carnitine carrier, which transports carnitine in a sodium-dependent fashion and which has a high expression in kidney) binds to OCTN2 on the luminal surface of renal proximal tubular cells [1].

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