Call for applications: Scholarships for doctoral MD students in the RTG 2578 (Promotionsstipendien für Medizin-Studierende)

1. Project

Project:	MD thesis within project 1b
Title:	Impact of hyperammonemia-induced osmotic and oxidative stress on genome/DNA integrity and neurogenesis of postnatal hippocampal neural stem/progenitor cells
Name of PI(s):	Prof. Dr. Orhan Aktas, Dr. Tim Prozorovskiy, PD Dr. Carsten Berndt
Institute:	Molecular Neurology/Thiology, Department of Neurology, Medical Faculty

Background: Acquired and inherited disorders that are characterized by an insufficient detoxification of ammonia result in hepatic encephalopathy. Hyperammonemia is associated with decreased intellectual properties including learning and memory deficits. Among the main factors by which ammonia neurotoxicity is considered to elicit neurological alterations are hyperosmotic shock and oxidative stress. Our ongoing study provide the first proof that acute hyperammonemia impairs proliferation and neurogenesis of cultivated hippocampal NSPCs and in mice administered with ammonia. Recent findings from other groups demonstrate the occurrence of DNA damage in the hippocampus following acute liver injury in the rodent model of hepatic encephalopathy. We hypothesize that genotoxic effects of hyperosmolarity/ROS production may potentially contribute to impairment of NSPC function upon hyperammonemia. In addition, hyperosmotic conditions have a major impact on chromatin re-organization and induce adaptive gene expression programme leading to growth arrest. Among chromatin modifiers, we have previously associated histone deacetylase SIRT1 with adaptation to oxidative stress. However, it is not known, weather SIRT1 plays a role in ammonia-induced chromatin alterations and DNA repair.

Aims: 1) Characterization of the DNA damage and DNA damage responses in postnatal hippocampal NSPCs following exposure to pathophysiological levels of ammonia relevant for hepatic encephalopathy. 2) Characterization of the impact of hyperosmotic/oxidative stress conditions on chromatin reorganization and posttranslational histone modifications in proliferating and differentiating murine NSPCs.

Experimental procedure / work programme: 1) Application of physiologically relevant concentrations of ammonium chloride/ammonium acetate to mitotically active NSPC and hippocampal slice cultures to analyze i) DNA damaging processes, ii) activation of stress-response kinases and iii) cell cycle arrest. 2) Analysis of SIRT1 activity and SIRT1 targets relevant for osmotic induced DNA damage/cell cycle arrest and chromatin reorganization during hyperammonemia.

Requirements: The ideal MD candidate is motivated to work in the fields of biochemistry and cell culture and interested in neurology and cell signaling.

2. Project

Project: MD thesis within project 5a
Title: Characterization of anthracycline-induced stress responses of early cardiovascular progenitor cells of murine and human origin
Name of PI(s): Prof. Dr. Gerhard Fritz
Institute: Institute of Toxicology, Medical Faculty

Background: Irreversible cardiotoxicity is a dose-limiting adverse effect of anthracyclines. The molecular mechanisms involved are still vague. Moreover, well-tolerated and effective cardioprotective measures are not available yet. It is believed that different cell types of the heart (i.e. cardiomyocytes, fibroblasts, endothelial cells) contribute to the pathophysiology of doxorubicin (Doxo)-evoked cardiac failure. Moreover, heart progenitor cells also seem to be of relevance in the pathogenesis of Doxo-induced heart injury. Of note, it appears feasible that the impact of different cardiac cell types and/or progenitor cells on the development of anthracycline-driven cardiotoxicity differs between the acute and chronic situation, leading to an additional and tremendous increase in complexity.

Aim: Here, we aim to characterize the response of early cardiovascular progenitor cells (CPC) of rodent and human origin to the anthracycline derivative doxorubicin and other cardiotoxic control substances, (i.e. ionizing radiation, imatinib). Moreover, the influence of selected cardioprotective candidate substances (i.e. statins, dexrazoxane) on the CPC´s stress responses will be investigated. We hypothesize that (i) stem and progenitor cells differ from each other in their response to genotoxic anticancer therapeutics and (ii) the stress responses provoked are agent- and species-specific.

Experimental approach and methods: Mouse embryonic stem cells (mESC), human induced-pluripotent stem cells (hiPSC) as well as early cardiovascular progenitor cells (mPC, hPC) will be used as *in vitro* model systems. mPC/hPC will be derived from the corresponding stem cells by initiation of the differentiation process employing small-molecule cocktails and/or growth factors. The various cell lines with be treated with the aforementioned cardiotoxic anticancer therapeutics (i.e. single (acute) and repeated (chronic) treatment) and cellular responses will be recorded. To this end, cell viability (Alamar blue and Neutral red assays (determination of IC_{50})), proliferation activity (mitotic index), cell death (apoptosis), DNA damage (DNA double-strand breaks) and gene expression (selected genes coding for factors regulating DNA repair, apoptosis, autophagy, senescence, proliferation) will be investigated in dose- and time kinetic analyses. Finally, the outcome of a co-treatment of the stem and progenitor cells with Doxo plus a selected (cardioprotective) candidate drug will be investigated to figure out whether protection by these drugs comprises both mESC, hiPSC and related mPC/hPC as hypothesized.

3. Project

Project:	**MD thesis within project 5b**
Title:	Interplay of mitochondrial quality control and drug-sensitivity in induced pluripotent stem cells (iPSCs)
Name of PI(s):	Prof. Dr. Andreas Reichert
Institute:	Institute of Biochemistry & Molecular Biology I, Medical Faculty

Background: The differentiation of stem cells to specific cell-types is tightly regulated and involves major metabolic adaptations. Also, the maintenance of stemness and the stable commitment of lineage during differentiation is strongly correlated to metabolic adaptations and changes of mitochondrial activities. In somatic cells, malfunction induced by genotoxic noxae is accompanied with a pleiotropy of harmful consequences which are linked to human diseases and ageing. The role of mitochondrial functions during pluripotency and lineage commitment as well as the role of mitochondrial quality control (mQC) in influencing these pathways is largely unknown.

Aim/Approach: Here, we plan to test whether modulation of metabolism/mitochondrial function and mQC in pluripotent stem cells and/or differentiating cells might influences their sensitivity to sub-lethal doses of genotoxic compounds or irradiation. For this work, we plan to focus on endothelial cells and/or cardiomyocytes derived from human iPSCs as a model system. We will apply a broad set of state-of-the-art biochemical and (live-cell) imaging methods. In sum, we are hoping to better understand the role of mitochondrial and metabolic changes during differentiation in genotoxins-exposed cells and to get further insights into possible pathomechanisms.