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

2023

1. Project	
Project:	MD thesis within project 1c
Title:	Investigations on DNA repair capacities of human neural progenitor cells (NPC) depending on the degree of differentiation and cell type
Researchers:	Prof. Dr. Ellen Fritsche (PI), Melanie Pahl (PhD student)
Institute:	Leibniz Research Institute for Environmental Medicine

Background: The development of the human brain is based on a variety of strictly regulated and time-dependent processes up to young adulthood. Early stages of **brain development** are characterized by extensive **proliferation of human neural stem- and progenitor cells** (NSPCs), which later on **differentiate** into neurons, oligodendrocytes and astrocytes. Furthermore, apoptosis is a key hallmark of human brain development as a large proportion of generated cells die during development. DNA-damaging substances can potentially disturb the balance of these processes by causing mutations that induce apoptosis, disturb differentiation or inhibit cell proliferation.

The type of **DNA damage** and therefore also the necessary DNA repair mechanism can thereby differ depending on the substance. However, the extent to which human NSPCs can be damaged by **genotoxic substances** and how their vulnerability changes during development have not been well studied. Since the developing cell types of the brain are of high longevity and their self-renewal capacity is limited during adulthood, it is particularly important that **DNA repair** is error-free. Exposure of pregnant women to cigarette smoke for example can lead to an increased rate of DNA adducts in umbilical cord blood and to impaired cognitive development of exposed children.

Within the '**Neurosphere Assay'**, a primary *in vitro* cell culture model based on human neural progenitor cells, which mimics a variety of neurodevelopmental processes, e.g. NPC proliferation, migration and differentiation into neural effector cells (astrocytes, neurons and OL), we already identified distinct effects of four different genotoxins. The quality and magnitude of effects thereby differ depending on the substance, treatment time point and the affected cell types.

Aim: To gain a better understanding of the different susceptibility toward genotoxins, this project is orientated to unravel their underlying molecular mechanisms. Therefore, immunocytochemical stainings and gene expression analyses of DNA damage response and DNA repair proteins will be performed. Moreover, pharmacological co-treatments will be used to rescue genotoxic damage. The results of these studies will contribute to a deeper understanding of developmental stage and cell type-specific susceptibility towards genotoxins during human brain development.

2. Project

Project:	MD thesis within project 1e
Title:	Characterization of bulk and selective autophagy in iPSC lines
Researchers:	Prof. Dr. Björn Stork (PI), Seda Akgün (PhD student)
Institute:	Institute of Molecular Medicine, Medical Faculty

Project description

Autophagy mediates the recycling of long-lived or damaged proteins or organelles. It plays an important role in stem cell populations in particular, as these cells depend on intracellular quality control and the maintenance of cellular homeostasis. During cellular reprogramming, cells are required to remove somatic features and to establish stemness. However, the role of autophagy during iPSC maintenance is not well defined.

In this project, the functional relevance of autophagy for **iPSC maintenance** should be characterized. For that, different iPSC lines will be treated with autophagy-inducing or autophagy-inhibiting compounds. Next to bulk autophagy induction by starvation (EBSS medium) or mTOR inhibition, we will employ small molecules specifically activating the autophagy-inducing ULK1 and PIK3C3/VPS34 complexes (BL-918 and LYN-1604 for ULK1; Tat-Beclin 1 peptide for PIK3C3/VPS34). With regard to autophagy inhibition, we will employ inhibitors of early (ULK1 inhibitors SBI-0206965 or ULK-101; PIK3C3/VPS34 inhibitors SAR405 or VPS34-IN1) and late stages of autophagy (bafilomycin A1). Autophagy will be monitored by immunoblotting and immunofluorescence according to established protocols in our lab. Furthermore, also selective autophagy processes should be investigated in this project. Here, we will mainly focus on **nucleophagy**, which selectively targets nuclear material for autophagic degradation. Next to the detection of autophagy, the pluripotency and stability of iPSCs will be confirmed by Oct4/Nanog immunofluorescence and karyotype analysis, respectively.

Collectively, we hope to elucidate the relevance of both bulk and selective autophagic processes during iPSC maintenance.

Requirements

Previous experience in laboratory work would be an advantage. However, more important are interest, scientific curiosity, motivation and the ability to work in a team.

Further reading

The signal transduction of autophagy represents the major research focus of Björn Stork's group.

Published work of our group can be fund under https://orcid.org/0000-0002-4167-7806

3. Project

Project: MD thesis within project 3a
Title: Impact of hemato-oncological therapies on genomic stability & differentiation capacity of human bone marrow-derived mesenchymal stromal cells in the context of therapy-related hematopoietic insufficiency and development of secondary myeloid
Researchers: PD Dr. Thomas Schroeder (PI), Bo Scherer (PhD student)
Institute: Clinic for Hematology, Oncology and Clinical Immunology

Background: Background: Hematotoxicity and development of therapy-related myeloid neoplasms (tMN) are common side effects of antineoplastic therapies like chemotherapy, radiation and small molecules causing relevant morbidity and mortality. Acknowledging the pivotal role of mesenchymal stromal cells (MSC) for the regulation of healthy hematopoiesis, we hypothesize that antineoplastic therapies impair genomic stability and differentiation of MSC thereby contributing to the development of hematopoietic insufficiency and tMN.

The project aims to comprehensively characterize the effects of antineoplastic therapies on functionality of healthy bone-marrow derived MSC including phenotype, genotype, differentiation and hematopoietic support function. Results from this project should enable a better understanding of underlying mechanisms and help to develop strategies to ameliorate incidence and severity of hematotoxicity as well as the risk of tMN.

Aim: Coming soon!

4. Project

Project: MD thesis within project 5b
Title: Interplay of mitochondrial quality control and drug-sensitivity in induced pluripotent stem cells (iPSCs)
Researchers: Prof. Dr. Andreas Reichert (PI), Michelle Westerhoff (PhD student)
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.