Universität Basel

Research Project

Cellular aging in-a-dish: Impact of stress

Third-party funded project

Project title Cellular aging in-a-dish: Impact of stress
Principal Investigator(s) Eckert, Anne ;
Organisation / Research unit
Bereich Psychiatrie (Klinik)
Bereich Psychiatrie (Klinik) / Erwachsenenpsychiatrie UPK
Department
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Aging is a risk factor for several of the world's most prevalent diseases, including neurodegenerative disorders. However, while much research has focused on age-related neurodegenerative disorders broadening our understanding of the underlying disease-specific molecular pathways, significantly fewer studies investigated the molecular biology of the aging brain in the absence of disease. Practical tools for studying brain aging encompass many model organisms. Since mouse models have some limitations regarding transferability to human physiology and lifespan, advanced human *in vitro* models are wanted. The fact that live human brain samples, such as neurons, are not as accessible slowed down progress in the field. The recent advent of technologies that enable adult human somatic cells to be reprogrammed into induced pluripotent stem cells (iPSCs) for the generation of neural cells as well as direct conversion into neural cells (induced neurons, iNs) has therefore provided a unique opportunity to investigate important aspects of CNS function *in vitro*. In contrast to iPSCs derived neurons, directly programmed iNs generated from aged donors' fibroblasts retain age-associated transcriptional signatures of the donor population and exhibit functional deficits in their capacity to properly compartmentalize nuclear and cytoplasmic proteins (Mertens et al., 2016, Mertens et al., 2015) suggesting that direct cell fate conversion bypassing pluripotency allows the identification of processes associated with aging and the modeling of human aging on a cellular level. However, many aging aspects were not yet investigated in this iNs model. Different hallmarks are generally considered to contribute to the aging process, e.g. mitochondrial failure, genomic instability, and telomere attrition. Together they determine the aging phenotype.

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The goal of the present proposal is therefore to further characterize and validate this advanced human neural *in vitro* model of aging by investigating

six important age-related candidate features: i) in the first place we focus on mitochondrial dysfunction as a central player in the aging process, where many age-associated impairments converge on with a negative impact; ii) genome instability, iii) telomere attrition, iv) epigenetic alterations, v) loss of proteostasis, and vi) cellular senescence;

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in three different aging models: a) the classic cell model of normal human fibroblasts (NHFs) from healthy young and aged donors, b) the advanced cell model of human induced neurons (iNs) from the corresponding young and aged donor fibroblasts, c) neuronal aging in the mouse brain (the Thy1-mitoCFP mouse model expressing the cyan fluorescent protein only in neuronal mitochondria, especially in the hippocampus, allows the comprehensive analysis of age-related changes in mitochondrial morphology and dynamics).

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Thus the study will address the following questions:

– Do iNs retain important aging-related signatures besides the donor-age dependent transcriptomic signature demonstrated by Mertens et al. (2015)?
– Are stress approaches effective in mimicking cellular aging in iNs?
– Are the aging signatures of iNs relevant for the aging brain?

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Our study will increase our understanding of how well “aged” iNs are representative of human aging by modeling the aging process *in vitro*. The more complete the aging phenotype of the “aged” iNs model is, the better it can be establish as an unprecedented tool for new drug discoveries to maintain healthy brain aging that may also prevent various age-related brain disorders.

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