Elucidating the effects of ageing on the nucleoporin-directed neural cell type-specific nuclear architecture and gene regulation

Fact Sheet

Project Information

EAGER
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Project website
Funded under H2020-EU.1.1.
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Hosted by DEUTSCHES ZENTRUM FUR NEURODEGENERATIVE ERKRANKUNGEN EV Germany

Start date 1 March 2019
End date 29 February 2024

Status Ongoing project

Project description

Ageing and some of its pathologies may be related to a cellular identity crisis

A membrane-bound nucleus is what defines eukaryotic cells. To traffic macromolecules between the nucleus and the cytoplasm, the nuclear envelope has huge nuclear pore complexes (NPCs) consisting of more than 1 000 protein subunits in humans called nucleoporins. These NPCs are extremely long-lived and remain incorporated in the nuclear membrane for the entire life of the cell. Defects in
nucleoporins play a role in cancer and ageing, and recently a link was found between nucleoporins, a key gene regulator and maintenance of cell identity in neural progenitor cells (that differentiate into neurons and glial cells). The EU-funded EAGER project is investigating the complicated relationship between cell type-specific gene regulation, cellular identity and ageing and disease.

**Objective**

Ageing is one of the most critical risk factors for neurological and psychiatric diseases. However, the biological links between physiological ageing and pathological development are still largely unknown. A solid understanding of the biology of brain ageing will thus be a key to developing the means to treat these diseases. Since neurons in the brain are mostly generated during development with limited capacity of replacement after birth, they need to maintain their identity and function throughout our lives. This project aims at seeking a link between the fundamental mechanism underlying the long-term maintenance of neural identity and effects of ageing on that.

We recently discovered that a cell type-specific nuclear architecture organized by nucleoporins in cooperation with a key transcription factor (TF), work as a structural gatekeeper for the maintenance of neural progenitor cells (NPs). Strikingly, nucleoporins are the most long-lived proteins in a cell and are known to be damaged during brain ageing. Thus, the proposed experiments will test a specific hypothesis that the nucleoporin-TF directed nuclear architecture is a fundamental principle governing cell type-specific gene regulation, and that pathological ageing impairs that critical relationship.

To test this hypothesis, we will use interdisciplinary approaches. First, the changes of molecular constituents of nucleoporin-TF partnerships from NPs into the post-mitotic neurons are probed. Second, the roles of identified partnerships in the maintenance of neuronal identity and function will be investigated using biochemical, imaging, genome-wide and behavioural approaches. Efforts will be directed toward studying the effects of ageing and Alzheimer’s diseases on the identified mechanisms. The successful completion of this research will uncover a novel aspect of regulation in the maintenance of cellular identity and open up a new field of research in neuroscience.

**Programme(s)**

**Topic(s)**

**Call for proposal**
Funding Scheme

ERC-STG - Starting Grant

Host institution

DEUTSCHES ZENTRUM FUR NEURODEGENERATIVE ERKRANKUNGEN EV

Address

Venusberg-campus 1/99
53127 Bonn
Germany

Activity type

Research Organisations

EU contribution

€ 1 499 998,75

Website

Contact the organisation

Beneficiaries (1)

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