Project 1.3. Targeting senescent brain cells to improve cognitive function in animal models of ageing and depression

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Background:

Ageing is a very complicated biological process that leads to weakening of organismal function, age-related diseases and finally death. There are many cellular and molecular mechanisms underlying ageing. Ageing is influenced by genetic factors as well as lifestyle and the environment. With age, senescent cells accumulate in the body and in tissues affected by age-related diseases. Cell ageing is a process that leads to many morphological and functional changes in a cell, including decreased sensitivity to factors causing cell death. Cellular senescence can be induced by any chemical, physical or mental stress. It is caused by damage to macromolecules, primarily to DNA. The signal of these lesions is cascaded to various molecules that modulate cellular processes. Senescent cells are fully functional and they secrete various factors into the microenvironment, give rise to chronic, sterile inflammation. Chronic inflammation contributes to many ageing-related diseases, including depression in the elderly. Studies of recent years, using genetically modified mice, have shown that removal of senescent cells from the animal's body weakens or eliminates ageing-related diseases. Several synthetic and natural compounds are already known that can exert such effect and they are called senolytics (from the words senescence and -lytic, "destroying"). We assumed that senolytics acting on senescent brain cells can affect neuronal plasticity, which will improve memory and reduce depression in the studied animals. In our study we decided to use old rats, which similarly to ageing humans, are more prone to depression. We will also use a special mouse model of the depressive state. Our preliminary results indicate that treating aged rats with senolytics improves their spatial memory. Our experiments to date, on nerve cells grown in vitro, have identified biomarkers of neuronal senescence.

Aim:

In the project we aim to investigate whether treating animals with senolytics to improve cognitive abilities and mood is directly related to the rejuvenation of nerve cells and brains. And whether this is associated with improvement of neuronal plasticity, which can be observed as changes in the structure of the dendritic tree and the structure and function of synapses. Senolytics can also indirectly improve neuronal function by eliminating senescent glial cells, which we are also going to check. If our assumptions are confirmed then our research may significantly contribute to opening new options for treatment of depression and alleviation of memory loss with age.

Requirements: For the implementation of the project we will use cell culture technique, molecular biology techniques, visualization techniques using light and confocal microscopy, bioinformatics methods and behavioral and memory tests. Thus the experimental background in at least two above mentioned techniques is required.