EXECUTIVE SUMMARY

Project: Clusterin as a new therapeutic target to improve clearance of vascular amyloid

PN-III-P4-ID-PCE2020-1622

Project manager – Prof Roxana Cărare

The overall aim of this proposal was to demonstrate that Clusterin is a key molecule that improves intramural periarterial drainage. The hypotheses tested within the University Medicine, Pharmacy, Science and Technology "George Emil Palade" Targu Mures using state of the art in vivo and microscopy techniques were:

1. The absence of clusterin results in a failure of IPAD of Aβ in $Clu^{-/-}$ mice;
2. Recombinant clusterin prevents/ameliorates the deposition of Aβ in the APP/PS1model of Alzheimer's disease.

These hypotheses were the first to address the potential for Clusterin as a chaperone that facilitates the intramural periarterial drainage of Aβ. So far, the project leader has demonstrated the failure of IPAD with increasing age, with posesison of APOE4 genotype and after immunization against Aβ.

In the final stage of the project we achieved the following:

1. In vitro analysis of IPAD to better understand the relationship between Clusterin and IPAD. This resulted in a manuscript submitted for publication in Scientific Reports, Impact Factor 4.6 (Q1).
2. Both APP/PS1 and Clusterin knock-out mice have been genotyped and colonies are currently at UMFST.
3. Experiments for IPAD analysis in the presence/absence of Clusterin have been completed.
4. Experiments to analyze the effect of Clusterin in the severity of amyloidosis in APP/PS1 have been completed.
5. The progress of the project in the context of progress in BA research was presented during the international conferences AAIC July 2023, VasCog September 2023, the research days of UMFST Târgu Mureș 5-10 Dec 2022 and will be presented also during the UMFST Târgu research days Mureș 12-15 Dec 2023.

Conclusions:

1) The percentage of capillaries with amyloid+CLU injected intracerebral is increased compared to the percentage of capillaries with simple amyloid injected intracerebral;
2) The percentage of arterioles with amyloid+CLU injected intracerebral is low compared to the percentage of arterioles with simple amyloid injected intracerebral;
3) These results will be validated with one-way ANOVA statistical tests, but suggest that the treatment with CLU results in a reduced capacity of the capillaries to drain the amyloid that does not reach the arteriolar walls;
4) The group of old mice that has a low percentage of amyloidosis is mixed, consisting of both treated and untreated mice, and within the group of young mice, there is no difference in the effect of the treatment
5) These results, which will have to be validated with statistical t-tests, suggest that the treatment effect is mixed and only in amyloidosis. A potential preventive effect could be observed in young transgenic mice that should be allowed to age for 3 months.

The project results indicate:

a) a beneficial effect of clusterin in combination 1:10 with amyloid beta 1-40 in the efficiency of amyloid drainage.
b) reduction of amyloidosis in some old transgenic animals treated with intraperitoneal clusterin. This effect will have to be validated and confirmed by statistical analysis.

Project Manager

Prof. Roxana Carare