RELAZIONE FINALE 1° ANNO DI DOTTORATO

Al collegio docenti del Dottorato in Medicina Molecolare

Dott. Lorenzo Guidotti

Ciclo: XXXVIII°

Tutor: Prof. Massimo Dal Monte

Scientific report (1st year of PhD Fellowship), academic year 2023/2024

Introduction

Nowadays, neurodegenerative diseases are increasingly worldwide due to the growing life expectancy and several environmental and genetic factors. One of the main neurodegenerative diseases is Alzheimer's disease (AD). AD is characterized by the accumulation of beta-amyloid and tau proteins which are able to induce over time death of neurons and loss of synapses, leading to a gradual and irreversible loss of cognitive functions with the development of classic symptoms such as loss of memory and empathy, disorientation, irascibility, anxiety, and spatial memory deficits. Unfortunately, the underlying molecular and physio-pathological mechanisms are still partially unknown. To shed light on them, my research activity in the first PhD year was based on the functional and molecular characterization of a murine model of familial AD (5xFAD) which reproduces over time the main hallmarks of this pathology. In particular, we choose to analyze the retina of 5xFAD mice since it is a dislocated part of the central nervous system, more easily accessible than the brain, in which typical AD alterations can be observed as in the brain, often earlier than in the brain.

Methods

- Experimental murine model: 5xFAD
- Scotopic, photopic, and pattern electroretinogram (ERG): evaluation of visual functionality
- Optical coherence tomography (OCT): evaluation of retina structure
- Ocular surgery and retinal dissection
- Molecular analysis: Western blot, RT-PCR, genotyping, and immunohistochemistry (on whole retinas or retina cryo-sections)
- Bioinformatic analysis on miRNome

Results

The electroretinographic analysis revealed that 5xFAD mice undergo a progressive loss of visual function over time. In particular, 3-month-old mice showed normal visual activity, 6-month-old mice bary dysfunction at the photoreceptor level while in 9-month-old mice not only the photoreceptor layer was affected but also the post-photoreceptor layers, indicating a massive loss of visual functionality. The preliminary structural analyses do not show any significant differences in 5xFAD mice. This could suggest that the loss of visual function precedes the anatomical alteration of the retina. The molecular analyses have demonstrated that in the early stages, there are no alterations in the inflammatory and oxidative stress pathways. Moreover, there are no differences in the level of microglia activation and macroglia reactivity. Collectively, these analyses suggest that at early stages 5xFAD mice do not show any functional, morphological, or molecular alteration. Further analyses will be necessary to investigate possible differences at later stages.

Congress

73rd Congress of the Italian Society of Physiology (SIF), Pisa, September 6-8, 2023. Poster Session:

Title: NaHS protects against cisplatin-induced cytotoxicity in HEI-OC1 cells

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Abstract: Cisplatin is a chemotherapeutic agent utilized for the treatment of several solid tumours. However, its clinical use is limited due to its nephrotoxicity, neurotoxicity, and ototoxicity. The observed toxicity is attributed to DNA cross-linking, increase of reactive oxygen species, and/or decline in cell antioxidant defenses. The aim of the work was to study the effect of sodium hydrosulfide (NaHS) on the auditory HEI-OC1 cells treated with cisplatin. NaHS acts as an H2S donor and has been shown to possess neuroprotective effects. Cell viability was assessed using the MTT assay, while caspase and sphingomyelinase activity were measured by a fluorometric and colorimetric method, respectively. Expression of transcription factors and genes encoding antioxidant response proteins were measured by western blot or RT-PCR, respectively. The combination of cisplatin plus NaHS resulted in increased cell viability of cisplatin-treated cells, and reduced the activity of acid sphingomyelinase, caspase-3, and caspase-9. In addition, the combined treatment increased the transcriptional levels of heme oxygenase 1, superoxide dismutase 2, NAD(P)H quinone dehydrogenase type 1, and the catalytic subunit of glutamate-cysteine ligase. The results suggest that NaHS counteracts the cytotoxic effect of cisplatin by enhancing the antioxidant response, and by reducing both acid sphingomyelinase and caspase activity.

Courses

- "**I finanziamenti europei nel settore digitale**", May 11, 10:00-13:00 (**0.5 CFU**)
- "**Europrogettazione: programmi, progetti e rendicontazione**", May 18, 10:00-13:00 (**0.5 CFU**)
- "**Science and Society: continuity and change**", May 29, 10:00-13:00 / 14:30-17:30 (**1 CFU**)
- "**PhD and then? Overview on career paths inside the academia**", June 8, 10:00-13:00 (**0.5 CFU**)
- "**Comunicare in ricerca**", June 21, 10:00-13:00 / 14:30-17:30 (**1 CFU**)
- "**Lavoro editoriale per l'editoria scolastica e universitaria (scienze e lettere)**", June 22, 10:00-13:00 / 14:30-17:30 (**1 CFU**)
- "**Ricerche bibliografiche e open access & science**", September 14, 10:00-13:00 / 14:30-17:30 (**1 CFU**)

Scientific publication

- Curcio M., Cirillo A., Amato R., Guidotti L., Amantea D., De Luca M., Nicoletta FP., Iemma F., Garcia-Gil M. (2022). Encapsulation of Alpha-Lipoic Acid in Functional Hybrid Liposomes: Promising Tool for the Reduction of Cisplatin-Induced Ototoxicity. Pharmaceuticals (Basel). 2022 Mar 24;15(4):394. doi: 10.3390/ph15040394.