

RELAZIONE FINALE I° ANNO DI DOTTORATO

Al collegio docenti del Dottorato in Medicina Molecolare

Dott. Alberto Melecchi

Ciclo: XXXVII° Tutor: Massimo Dal Monte

Attività scientifica svolta nel 1°anno di Dottorato, Anno Accademico 2022/2023

Introduction

The research activity of the first PhD year focused on the study of the main physio-pathological mechanisms of high-incidence neurodegenerative diseases of the retina, such as Age-related macular degeneration (AMD), Diabetic Retinopathy (DR), Glaucoma, and their possible prevention following natural compounds administration. In these studies, in-vivo experimental models were used to reproduce (spontaneously or by induction) the main pathological hallmarks of these retinopathies.

Methods

- Experimental models of Dry AMD (Light-induced retinal damage in rats, subretinal injection of PEG-400 in mice), DR (induced by Streptozotocin in rats), and Glaucoma (DBA/2J mouse strain).
- Oral gavages, intraperitoneal injections;
- Ocular surgery and retinal dissection;
- Scotopic, photopic and pattern electroretinography (ERG) measurements to evaluate the visual functionality; Intraocular pressure (IOP) recordings by tonometry.
- Molecular analyses: Western blot, RT-PCR and Immunohistochemistry (on whole retinas or on retinal cryo-sections).

Results

Studies on experimental mouse and rat models of dry AMD and DR showed that the oral administration of different natural compounds with a strong antioxidant and anti-inflammatory activity, was able to prevent and/or counteract the neurovascular abnormalities. These findings highlight the crucial role of oxidative stress and inflammation in retinal neurovascular dysfunction and suggest a novel rationale for the treatment of such retinal diseases. In this respect, time-dependent analyses carried out on spontaneous mouse model of hypertensive glaucoma highlighted the alterations of the retinal neurovascular unit components in association with increased levels of IOP and retinal ganglion cells loss during the progression of this disease. These results would suggest the neurovascular unbalance as a crucial pathological event in glaucoma, similarly to what occurs in AMD and DR.

Congresses and courses attended:

- **72th Congress of the Italian Society of Physiology (SIF)**, Bari, September 14-16, 2022.
Poster session:
Title: *Neurodegeneration and vascular dysfunction: clues from a mouse model of glaucoma;*
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Abstract: Visual processing in the retina is dependent on intimate neurovascular relationship to ensure a proper metabolic supply to neurons. Alterations in neurovascular balance may initiate neurodegenerative processes leading to visual loss as in the case of glaucoma, in which elevated intraocular pressure (IOP) is commonly considered as the main cause of retinal ganglion cell (RGC) loss. However, time-dependent alterations in retinal vascularization and their influence on RGC death remain to be clarified. The aim of this study is to assess whether retinal vascular alterations concur with or follow RGC death in glaucoma progression. Here, we used the DBA/2J mouse as a spontaneous model of glaucoma to evaluate the time-dependent correlation between IOP increase, RGC loss and glial reactivity with possible vascular alterations. In DBA/2J mice, IOP elevation started at 6 months of age. The decrease in RGC density was evident 4 months later in concomitance with a gradual regression of retinal vasculature and increase in astrocyte gliosis. Conversely, Müller cells became activated earlier in concomitance with initial IOP elevation, suggesting their potential role in mediating the neurovascular breakdown. These findings demonstrate that impaired vasculature concurs with IOP elevation to induce RGC loss thus providing the basis for investigating whether impaired vasculature increases the sensitivity of RGC to elevated pressure.

- ***Soft Skills courses:***

19 maggio 9.00-13.00 - Ricerche bibliografiche e open access & science;
 27 maggio 9.00-12.00 - Diritto dei brevetti;
 30 maggio 8.30-12.30 / 14.30-18.30 - Spin Off e Start up della ricerca: concetti introduttivi e presupposti per la nascita di un'impresa; 31 maggio 8.30-12.30/14.30-18.30 - Spin Off e Start up della ricerca: Il modello di business e i regolamenti;
 7 giugno 10.00-13.00 - Spin Off e Start up della ricerca: L'ecosistema di innovazione a supporto delle start up;
 13 giugno 9.00-13.00/14.00-16.00 - Creating value from large archive and big data;
 15 giugno 9.00-13.00/14.00-18.00 - I rapporti tra scienza e società: tra persistenze e cambiamenti;
 20 giugno 09.00-13.00/14.00-18.00 - Comunicare in ricerca;
 27 giugno 10.00-13.00 - Fare ricerca per l'inclusione sociale;
 1 luglio 9.00-13.00/14.00-18.00 - Lavoro editoriale per l'editoria scolastica e universitaria (scienze e lettere);
 7 e 8 settembre 9.00-13.00 - Il ruolo della standardizzazione nei processi di innovazione;
 22 e 23 settembre - How to exploit your research idea: a quick introduction to EU project design and management.

- ***Italian Platform on Alternative Methods (IPAM in silico 2022) courses:***

- *Corso teorico-pratico sull'applicazione dei metodi computazionali nel Replacement*, 5 modules = 20 hours, May, 9th – June, 6th, 2022.
- 3Rs-3days webinar cycle Replacement, Reduction, Refinement February, 7th -14th -21st 2022

- ***Istituto Zooprofilattico Sperimentale della Lombardia e dell'Emilia Romagna “Bruno Ubertini” (IZSLER) courses:***

- *Elementi base per l'approccio dei ricercatori all'utilizzo degli animali ai fini scientifici- Edizione Unica*; January, 24th – November, 30th, 2022 (13 crediti formativi).
- *Legislazione nazionale ed etica livello 1, moduli 1 e 2, DM 5 Agosto 2021 – Edizione Unica*; Corso accreditato presso il Ministero della Salute ai sensi del DM.5 Agosto 2021; May, 30th –November, 30th, 2022 (7,5 crediti formativi).

Scientific publications:

- Amato R., Canovai A., Melecchi A., Pezzino S., Corsaro R., Dal Monte M., Rusciano D., Bagnoli P. and Cammalleri, M. (2021). *Dietary Supplementation of Antioxidant Compounds Prevents Light-Induced Retinal Damage in a Rat Model*. Biomedicines, 9(9), 1177. <https://doi.org/10.3390/biomedicines9091177>
- Canovai A., Amato R., Melecchi A., Dal Monte M., Rusciano D., Bagnoli P. and Cammalleri, M. (2022). *Preventive Efficacy of an Antioxidant Compound on Blood Retinal Barrier Breakdown and Visual Dysfunction in Streptozotocin-Induced Diabetic Rats*. Frontiers in Pharmacology, 12, 811818. <https://doi.org/10.3389/fphar.2021.811818>
- Melecchi A., Amato R., Lapi D., Dal Monte M., Rusciano D., Bagnoli P. and Cammalleri M. (2022). *Increased efficacy of dietary supplement containing wax ester-rich marine oil and xanthophylls in a mouse model of dry macular degeneration*. Frontiers in Pharmacology. DOI: 10.3389/fphar.2022.1038730. **Accepted**