

RELAZIONE FINALE II° ANNO DI DOTTORATO

Al collegio docenti del Dottorato in Medicina Molecolare

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Ciclo: XXXVII° Tutor: Massimo Dal Monte

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Introduction

The research activity of the 2nd PhD year was based on the results obtained in the 1st year regarding the study of the main physio-pathological mechanisms of high-incidence neurodegenerative diseases of the retina, such as Diabetic Retinopathy (DR) and 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

- DR (induced by Streptozotocin in rats), and Glaucoma (DBA/2J mouse strain or induced by Methylcellulose (MCE) intraocular injection).
- Intraperitoneal or subcutaneous 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 hypertensive Glaucoma and DR showed that the oral administration of different natural compounds with antioxidant and anti-inflammatory properties was able to prevent and/or counteract the neurodegenerative processes typical of both retinopathies. In particular, time-dependent analyses carried out on a 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 (RGC) loss during the disease, with an alteration of glial cells that occurs even before the hypertensive stage onset suggesting its potential role in increasing the susceptibility of RGC death. Moreover, studies carried out on a spontaneous mouse model of DR displayed a thyroid hormone signaling modulation following high glucose-induced stress, representing an adaptive response against metabolic imbalance but it might turn detrimental when DR enters chronic phases. These findings highlight the crucial role of oxidative stress and inflammation in retinal neurovascular dysfunction, in which retinal neurovascular unit unbalance represents a crucial pathological event in glaucoma and DR.

• Congress abstract

- **International Astrocyte School (IAS)**, Bertinoro, March 26-April 1, 2023. *Müller cell reactivity as an early event of retinal neurovascular breakdown in the DBA/2J mouse model of glaucoma*. **A. Melecchi**, A. Canovai, M. Cammalleri, G. Casini, M. Dal Monte, P. Bagnoli, V. Porciatti, R. Amato.
- **2nd Workshop Ophthalmic formulations: Challenges and Advances**, July 14, 2023, Pisa. *Efficacy of a spearmint (*Mentha spicata* L.) extract as nutritional support in a rat model of hypertensive glaucoma*. **A. Melecchi**, R. Amato, A. Canovai, S. Maci, M. Cammalleri, M. Dal Monte.
- **73rd Congress of the Italian Society of Physiology (SIF)**, Pisa, September 6-8, 2023. *Thyroid hormone signaling is involved in retinal response to high glucose: a double-edged sword*. **A. Melecchi**, F. Forini, M. Lulli, S. Balzan, G. Nicolini, A. Saba, A. Bertolini, E. Andreucci, S. Marracci, D. Terlizzi, R. Zucchi, G. Iervasi, R. Amato, G. Casini.

• Soft skills courses

- “Lezione 9: Europrogettazione: programmi, progetti e rendicontazione”; 18-05-23.
- “Science and Society: continuity and change”; Dr.ssa Agnes Allansdottir; 29-05-23.
- “PhD and then? Overview on career paths inside and outside the academia”; Prof. Gennaro Prota e Dott.ssa Aida Ribera Navarro; 12-06-23.

• Publications

- Minnelli C, Piva F, Cecati M, Armeni T, Mobbili G, Galeazzi R, **Melecchi A**, Cristaldi M, Corsaro R, Rusciano D. Meldonium Inhibits Cell Motility and Wound-Healing in Trabecular Meshwork Cells and Scleral Fibroblasts: Possible Applications in Glaucoma. *Pharmaceuticals (Basel)*. 2023 Apr 15;16(4):594. doi: 10.3390/ph16040594.
- Amato R, Cammalleri M, **Melecchi A**, Bagnoli P, Porciatti V. Natural History of Glaucoma Progression in the DBA/2J Model: Early Contribution of Müller Cell Gliosis. *Cells*. 2023 Apr 27;12(9):1272. doi: 10.3390/cells12091272.
- **Melecchi A**, Amato R, Dal Monte M, Rusciano D, Bagnoli P, Cammalleri M. Restored retinal physiology after administration of niacin with citicoline in a mouse model of hypertensive glaucoma. *Front Med (Lausanne)*. 2023 Sep 5;10:1230941. doi: 10.3389/fmed.2023.1230941.

- Forini F, Nicolini G, Amato R, Balzan S, Saba A, Bertolini A, Andreucci E, Marracci S, **Melecchi A**, Terlizzi D, Zucchi R, Iervasi G, Lulli M, Casini G. Local modulation of thyroid hormone signaling in the retina affects the development of diabetic retinopathy. *Biochim Biophys Acta Mol Basis Dis.* 2023 **Accepted.**
- Amato R, Canovai A, **Melecchi A**, Maci S, Quintela F, Fonseca B. A, Cammalleri M, Dal Monte M. Efficacy of a spearmint (*Mentha spicata L.*) extract as nutritional support in a rat model of hypertensive glaucoma. *Transl Vis Sci Technol.* 2023. **Under review.**
- Amato R, **Melecchi A**, Pucci L, Canovai A, Marracci S, Cammalleri M, Dal Monte M, Caddeo C, Casini G. Liposome-mediated delivery improves the efficacy of Lisosan G against retinopathy in diabetic mice. *Cells.* 2023. **Under review.**