DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO

Cycle XL

Project proposal for a PhD scholarship (with no financial support from Sapienza)

Title of the research: Study of neural stem cell reactivation in mouse models of aging and with defective neurogenesis

Supervisor: Dr. Felice Tirone (email: felice.tirone@cnr.it) https://publications.cnr.it/authors/felice.tirone
Istituto di Biochimica e Biologia cellulare- Consiglio Nazionale delle Ricerche – Via Ercole Ramarini 32 00015 Monterotondo Scalo - Roma

Co-supervisor: Dr. Laura Micheli (email: laura.micheli@cnr.it)
https://publications.cnr.it/authors/laura.micheli

Tutor: Prof. Adamaria Tata (email: adamaria.tata@uniroma.it)

Host Institution: Institute of Biochemistry and Cell Biology-CNR, Monterotondo, Rome

Summary

The research project concerns the study of neurogenesis processes in the brain of adult and aged subjects, through the use of specific mouse models. Particular attention is paid to the role of stem cells involved in these processes and to the possibility of their use as therapeutic targets. In addition, the cellular and molecular mechanisms involved are investigated.
In particular, the project is based on the following **Objective**:
Study of neurogenesis (i.e., production of new neurons from stem cells in the neurogenic niches of the dentate gyrus, DG, and sub-ventricular zone, SVZ) and of the effect of different neurogenic stimuli (e.g. voluntary running, administration of natural substances) in mouse models with defective adult neurogenesis (aged mice and p16Ink4a-ko).
This Objective includes the following tasks:
Task A) Molecular studies by RNA-sequencing of the neurogenic niches of mouse models in which neurogenesis is impaired in the aged animal (p16Ink4a-ko). We thus intend to identify genes whose activation is related to the reactivation of defective stem cells of neurogenic niches by physical exercise (running). We then aim to study in vitro and in vivo the function of the genes identified by RNAseq;
Task B) Cellular and behavioral studies in aged p16Ink4a-ko mice subjected to voluntary running. In 12-month-old mice belonging to this mouse model, voluntary running stimulates neural stem cells to come out of quiescence;
Task C) Molecular, biochemical, cellular and behavioral studies in mice treated with hydroxytyrosol (HTyr), a natural anti-oxidant component present in EVOO (extra virgin olive oil). HTyr stimulates the production of new neurons in adult and aged mice (D'Andrea et al., 2020). With these studies we will be able to verify the level of plasticity of the dentate gyrus stem cells and the possibility of reactivating it in defective cells or in aged animals, thus deducing indications on the self-renewal model even in old age.

References

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- *Kempermann G, Song H, Gage FH. Neurogenesis in the Adult Hippocampus. Cold Spring Harb Perspect Biol. 2015 Sep 1;7(9):a018812.*
- *de Pablos RM, Espinosa-Oliva AM, Hornedo-Ortega R, Cano M, Arguelles S. Hydroxytyrosol protects from aging process via AMPK and autophagy; a review of its effects on cancer, metabolic syndrome, osteoporosis, immune-mediated and neurodegenerative diseases. Pharmacol Res. 2019 May;143:58-72.*

Pertinent Publications of the proponent (last 5 years)

- *Micheli L, D'Andrea G, Ceccarelli M, Ferri A, Scardigli R, Tirone F. p16Ink4a Prevents the Activation of Aged Quiescent Dentate Gyrus Stem Cells by Physical Exercise. Front Cell Neurosci. 2019 Feb 7; 13:10.*
- *Micheli L, D'Andrea G, Creanza TM, Volpe D, Ancona N, Scardigli R, Tirone F. Transcriptome analysis reveals genes associated with stem cell activation by physical exercise in the dentate gyrus of aged p16Ink4a knockout mice. Front Cell Dev Biol. 2023 Oct 19;11:1270892. doi: 10.3389/fcell.2023.1270892.*
- *D'Andrea G, Ceccarelli M, Bernini R, Clemente M, Santi L, Caruso C, Micheli L, Tirone F. Hydroxytyrosol stimulates neurogenesis in aged dentate gyrus by enhancing stem and progenitor cell proliferation and neuron survival. FASEB J. 2020 Mar;34(3):4512-4526. doi: 10.1096/fj.201902643R.*
- *Ceccarelli M, D'Andrea G, Micheli L, Tirone F. Interaction Between Neurogenic Stimuli and the Gene Network Controlling the Activation of Stem Cells of the Adult Neurogenic Niches, in Physiological and Pathological Conditions. Front Cell Dev Biol. 2020 Apr 7; 8:211. doi: 10.3389/fcell.2020.00211. eCollection 2020. Review.*
- *Micheli L, Creanza TM, Ceccarelli M, D'Andrea G, Giacovazzo G, Ancona N, Coccurello R, Scardigli R, Tirone F. Transcriptome Analysis in a Mouse Model of Premature Aging of Dentate Gyrus: Rescue of Alpha-Synuclein Deficit by Virus-Driven Expression or by Running Restores the Defective Neurogenesis. Front Cell Dev Biol. 2021 Aug 17;9:696684.*
- *Micheli L, Bertini L, Bonato A, Villanova N, Caruso C, Caruso M, Bernini R, Tirone F. Role of Hydroxytyrosol and Oleuropein in the Prevention of Aging and Related Disorders: Focus on Neurodegeneration, Skeletal Muscle Dysfunction and Gut Microbiota. Nutrients. 2023 Apr 4;15(7):1767. doi: 10.3390/nu15071767.*