PROJECT

Supervisor:	Gianvito Martino
Title:	The role of IGFBPL1 secreted by endogenous neural stem cells in regulating age-related cognitive functions
Curriculum:	Molecular Medicine: Neurosciences and Experimental Neurology

Link to the personal page of the University or relevant hospital site website:

https://www.unisr.it/en/docenti/m/martino-gianvito

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Age-related cognitive decline has major socio-economic consequences and is associated with alterations in molecular pathways, synaptic organization, and reduced neurogenesis, leading to impaired function of the neural stem cell niche. Recent evidence indicates that adult endogenous neural precursor cells (eNPCs) in the subventricular zone not only support olfactory neurogenesis but also play a key role in maintaining striatal homeostasis. ENPCs modulate GABAergic transmission between parvalbumin-expressing fast-spiking interneurons and medium spiny neurons through the secretion of IGFBPL-1, which regulates IGF-1 signaling. Disruption of eNPCs or IGF signaling impairs intrastriatal coherence, synaptic transmission, and striatum-dependent behaviors. Human studies further support these findings, showing IGFBPL-1 expression in the SVZ and a correlation between SVZ damage, reduced striatal volume and cognitive deficits (Butti et al, 2022).

Rationale and hypothesis

We will investigate the molecular and cellular mechanisms underlying synaptic dysfunction and cognitive decline during aging with a specific focus on IGFBPL1. Aging-related reductions in neurogenesis, synaptic plasticity, and eNPC function—including decreased IGFBPL1 secretion—are hypothesized to disrupt striatal homeostasis and exacerbate cognitive decline. Given the paracrine effects of IGFBPL1 on striatal neurons and the neuronal alterations observed in IGFBPL1 KO, defining the role of IGFBPL1 and eNPC molecular

pathways in the aged brain may reveal novel therapeutic strategies to counteract brain aging and slow cognitive deterioration.

Objectives and specific aims

The main objective of this research is to explore the molecular mechanisms underlying age-related cognitive decline and evaluate potential therapeutic strategies to restore cognitive function in aging.

Aim 1:to investigate the morphological, neurophysiological, synaptic structure and gene expression changes that occur in the striatum during aging, focusing on and assessing how these modifications impact behavior and overall brain functions. **Aim 2:**defining the role of IGFBPL1 and elucidating the molecular mechanisms through which it regulates striatal homeostasis in young and aged IGFBPL1KO and NestinCre^{RT2}IGFBPL1flox/flox mice. **Aim 3:** to explore rejuvenation strategies aimed at restoring the functionality of the neurogenic niche and the striatal homeostasis, using gene therapy approaches.

Expected outcomes

The project therefore aims to achieve a deeper understanding of the characteristics of the neural niche during aging, paving the way for future clinical applications that could improve cognitive function and alleviate age-related brain disorders. By characterizing age-associated changes and investigating the underlying molecular mechanisms, it may be possible to elucidate the molecular and cellular dysfunctional processes occurring in eNPCs within the aging brain, thereby providing valuable insights for the development of targeted therapeutic interventions.

Skills that the student should acquire (max. 600 characters including spaces):

Handling transgenic mouse lines, administering in vivo injections using a stereotactic technique, conducting confocal microscopy, immunohistochemistry, immunofluorescence staining, rt-PCR, single cell RNA, spatial transcriptomic and bioinformatics analysis, administering compounds and drugs in vivo. Maintaining a thorough understanding of the latest literature in the field, constructing hypotheses, developing experimental plans to investigate these hypotheses, writing regular scientific reports, analyzing and discussing results, and critically evaluating published papers (e.g., Journal Club).

References (max. 15)

- Crimmins EM. (2021) Recent trends and increasing differences in life expectancy present opportunities for multidisciplinary research on aging. Nat Aging.

- Butti E, Cattaneo S, Bacigaluppi M, Cambiaghi M, Scotti GM, Brambilla E, Ruffini F, Sferruzza G, Ripamonti M, Simeoni F, Cacciaguerra L, Zanghì A, Quattrini A, Fesce R, Panina-Bordignon P, Giannese F, Cittaro D,

Kuhlmann T, D'Adamo P, Rocca MA, Taverna S, Martino G. (2022) Neural precursor cells tune striatal connectivity through the release of IGFBPL1. Nat Commun.

-Butti E, Bacigaluppi M, Rossi S., Cambiaghi M, Bari M., Cebrian Silla A, Brambilla E, Musella A, De Ceglia R, Teneud L, De Chiara V, D'Adamo P, Garcia-Verdugo JM, Comi G, Muzio L, Quattrini A, Leocani L, Maccarrone M, Centonze D and Martino G. (2012) Subventricular zone neural progenitors protect striatal neurons from glutamatergic excitotoxicity. Brain