DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO

Proposta di progetto per una borsa Dottorato Sapienza
Linea di ricerca principale

Titolo della ricerca: Molecular pathways regulating neural stem cell proliferation and differentiation.

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Summary
Mammalian brain function depends on complex neuronal networks, generated by producing appropriate neuronal numbers and types during development and adulthood. Neuron production, or neurogenesis, is carried out by neural stem cells (NSCs), specialized glial cells capable of proliferation and neuronal differentiation. Both in the embryonic and in the adult CNS, NSC are finely regulated, since both insufficient and excessive NSC proliferation and differentiation can exert detrimental consequences. NSC proliferation and differentiation need to be sufficiently stimulated to produce proper neuronal numbers, but also limited to prevent the NSC pool exhaustion. A delicate balance between signals stimulating or restraining NSC proliferation and differentiation takes place in the NSC environment to achieve optimal neurogenesis levels (Cacci et al. 2017; Lupo et al. 2019).

Tsukushi (TSK) is a secreted small leucine-rich proteoglycan, acting as an extracellular signalling regulator to control the development and homeostasis of various organs (Ohta et al., 2004, 2011). TSK is involved in brain development and in congenital hydrocephalus, a disorder due to the dilatation of the brain lateral ventricles. TSK-KO mice show hydrocephalus along with altered NSC proliferation and differentiation, suggesting that ventricle expansion in these mice might be caused by impaired NSC regulation. TSK point mutations, which are predicted to affect TSK tridimensional structure, have been found in hydrocephalus patients (Ito et al. 2021).

This project will aim to elucidate the mechanisms of TSK function in the control of NSC proliferation and differentiation, focusing on the molecular pathways regulated by TSK and on the effects of the hydrocephalus-associated TSK mutations on TSK function in NSC regulation. The project will also involve the study of the possible interactions of TSK with other extrinsic and intrinsic regulators of NSC proliferation and differentiation that are currently studied in the host lab. To this aim, the project will employ in vitro NSC model systems, on which the host lab has a consolidated expertise (Lupo et al. 2018).

Pertinent Publications of the proponent (last 5 years)

1: Di Nisio E, Lupo G, Licursi V, Negri R. The Role of Histone Lysine Methylation in the Response of Mammalian Cells to Ionizing Radiation. *Front Genet. 2021* Mar 30;12:639602.
2: Ito N, Riyadh MA, Ahmad SAI, Hattori S, Kanemura Y, Kiyonari H, Abe T, Furuta Y, Shinmyo Y, Kaneko N, Hirota Y, Lupo G, Hatakeyama J, Abdulhaleem M FA, Anam MB, Yamaguchi M, Takeo T, Takebayashi H, Takebayashi M, Oike Y, Nakagata N, Shimamura K, Holtzman MJ, Takahashi Y, Guillemot F, Miyakawa T, Sawamoto K, Ohta K. Dysfunction of the proteoglycan Tsukushi causes hydrocephalus through altered neurogenesis in the subventricular zone in mice. *Sci Transl Med. 2021* Mar 31;13(587):eaay7896.
3: Persiconi I, Cosmi F, Guadagno NA, Lupo G, De Stefano ME. Dystrophin Is Required for the Proper Timing in Retinal Histogenesis: A Thorough Investigation on the mdx Mouse Model of Duchenne Muscular Dystrophy. *Front Neurosci. 2020* Aug 31;14:760.

4: Licursi V, Anzellotti S, Favaro J, Sineri S, Carucci N, Cundari E, Fiore M, Guarguaglini G, Pippa S, Nisi PS, Vernì F, Biagioni S, Cacci E, Amendola R, Lupo G, Negri R. X-ray irradiated cultures of mouse cortical neural stem/progenitor cells recover cell viability and proliferation with dose-dependent kinetics. *Sci Rep. 2020* Apr 16;10(1):6562.
5: Poiana G, Gioia R, Sineri S, Cardarelli S, Lupo G, Cacci E. Transcriptional regulation of adult neural stem/progenitor cells: tales from the subventricular zone. *Neural Regen Res. 2020* Oct;15(10):1773-1783.
6: Lupo G, Gaetani S, Cacci E, Biagioni S, Negri R. Molecular Signatures of the Aging Brain: Finding the Links Between Genes and Phenotypes. *Neurotherapeutics. 2019* Jul;16(3):543-553.
7: Ajmone-Cat MA, Onori A, Toselli C, Stronati E, Morlando M, Bozzoni I, Monni E, Kokaia Z, Lupo G, Minghetti L, Biagioni S, Cacci E. Increased FUS levels in astrocytes leads to astrocyte and microglia activation and neuronal death. *Sci Rep. 2019* Mar 14;9(1):4572.
8: Lupo G, Gioia R, Nisi PS, Biagioni S, Cacci E. Molecular Mechanisms of Neurogenic Aging in the Adult Mouse Subventricular Zone. *J Exp Neurosci. 2019* Feb 19;13:1179069519829040.
9: Lupo G, Nisi PS, Esteve P, Paul YL, Novo CL, Sidders B, Khan MA, Biagioni S, Liu HK, Bovolenta P, Cacci E, Rugg-Gunn PJ. Molecular profiling of aged neural progenitors identifies Dbx2 as a candidate regulator of age-associated neurogenic decline. *Aging Cell. 2018* Jun;17(3):e12745.
10: Kawano R, Ohta K, Lupo G. Cadherin-7 enhances Sonic Hedgehog signalling by preventing Gli3 repressor formation during neural tube patterning. *Open Biol. 2017* Dec;7(12):170225.
11: Carucci N, Cacci E, Nisi PS, Licursi V, Paul YL, Biagioni S, Negri R, Rugg-Gunn PJ, Lupo G. Transcriptional response of Hoxb genes to retinoid signalling is regionally restricted along the neural tube rostrocaudal axis. *R Soc Open Sci. 2017* Apr 5;4(4):160913.
12: Guadagno NA, Moriconi C, Licursi V, D'Acunto E, Nisi PS, Carucci N, De Jaco A, Cacci E, Negri R, Lupo G, Miranda E. Neuroserpin polymers cause oxidative stress in a neuronal model of the dementia FENIB. *Neurobiol Dis. 2017* Jul;103:32-44.
13: Cacci E, Negri R, Biagioni S, Lupo G. Histone Methylation and microRNA-dependent Regulation of Epigenetic Activities in Neural Progenitor Self-Renewal and Differentiation. *Curr Top Med Chem. 2017*;17(7):794-807.