RESEARCH TOPIC MEM14
Role of Microglial receptor TREM2 in hypothalamic neurovascular unit intercommunication: regulations of energy homeostasis

Curriculum MEM standard

Research Area
Neuro

Laboratory name
Laboratory of Pharmacology and Brain Pathology

Research Supervisor
Michela Matteoli michela.matteoli@hunimed.eu

Abstract
Microglia are the main residential immune cells of the brain. Not only do they allow continuous communication between neuronal cells and the immune system but are emerging as fundamental components of the neurovascular unit – the physical barrier and gateway that separate the peripheral tissues from the brain parenchyma. Microglia cells control the metabolic homeostasis of different brain cells (Paolicelli et al., 2022). In particular, the Triggering Receptor Expressed on Myeloid cells 2 (TREM2), an immune receptor expressed in the brain microglia, has recently emerged as central in controlling the metabolic fitness of neurons in the developing hippocampus, in addition to directing synapse elimination and shaping the functional brain connectivity (Filipello, Morini et al., Immunity 2018; Tagliatti, Desiato et al., Immunity 2024). Given that mice lacking TREM2 display defects in systemic metabolism, we will investigate whether TREM2- bearing microglia play a role in tuning the functionality of the blood-brain / CSF-brain barriers at the hypothalamic levels. Indeed, these structures are primarily involved in many body functions including feeding control and systemic energy expenditure. We thus hypothesize that alterations in neuronal hypothalamic metabolism due to lack of trem2 may represent a crucial step in the development of metabolic diseases. By using a combination of transcriptomics analysis and cell-based imaging methods, we will characterize the influence of TREM2 expression on functional hypothalamic cell populations in a sex-specific manner. We will uncover how defective Trem2 impacts the transcriptomic profile, morphology, and function of selected neuronal cell populations and determine which subsets of microglia cooperate within hypothalamic centers. Data from this study will provide comprehensive knowledge of microglia functions in shaping hypothalamic complexity and endocrine output. Also, they will offer a targeting potential for new therapeutic strategies that could reverse immune-metabolic dysfunction by modulation of hypothalamic microglial function.

Main technical approaches

Project execution requires a multidisciplinary approach based on a combination of techniques including:

- molecular biology;
- confocal microscopy ;
-morphological and functional analysis of microglia and CNS synapses.

Bioinformatic analysis

-mouse behavior

The candidate will use a variety of experimental models:

-in vitro primary cultures from neurons, endothelial cells and glia

-ex vivo brain slices

-Transgenic mouse models

Scientific references

Filipello F, Morini R, Starvaggi C, Canzi A, Corradini I, Erreni M, Otero K, Piccio L, Perrucci F, Tamborini M, Rajendran L, Menna E, Vetrano S, Michalski B, Fahnestock M, Paolicelli R, Matteoli M (2018) The microglial innate immune receptor TREM2 is required for neuronal synapse elimination. Immunity 48(5):979-991

-Tagliatti E, Desiato G, Mancinelli S, Bizzotto M, Gagliani MC, Faggiani E, Hernández-Soto R, Cugurra A, Poliseno P, Miotto M, Argüello RJ, Filipello F, Cortese K, Morini R, Lodato S, Matteoli M. Trem2 expression in microglia is required to maintain normal neuronal bioenergetics during development. Immunity. 2024 Jan 9;57(1):86-105.e9. doi: 10.1016/j.immuni.2023.12.002. Epub 2023 Dec 29. PMID: 38159572; PMCID: PMC10783804.

Type of contract

PhD scholarship of € 21.000 gross per year awarded by Humanitas University. This sum is exempt from IRPEF income tax according to the provisions of art. 4 of Law no. 476 of 13th August 1984, and is subject to social security contributions according to the provisions of art. 2, section 26 and subsequent sections, of Law no. 335 of 8th August 1995 and subsequent modifications.

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Humanitas University
Via Rita Levi Montalcini, 4
20072 Pieve Emanuele (MI) Italy
Tel +39 0282241 - Fax +39 0282242394
info@hunimed.eu
hunimed.eu
CF 97692990159