PROJECT

Supervisor:	Cinthia Farina
Title:	Checkpoints for CNS inflammation
Curriculum:	Neurosciences and Experimental Neurology
Link to the personal page of the University or relevant hospital site website:	https://research.hsr.it/en/institutes/institute-of-experimental-neurology/immunobiology-of-neurological-disorders.html

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

Background/gap of knowledge

Multiple Sclerosis (MS) is the most common cause of neurological disability in young adults. It is a chronic inflammatory disorder of the central nervous system (CNS) characterized by demyelination, inflammation and neuroaxonal damage. To counteract MS, therapies must target the immune system- to reduce inflammation- and the nervous system- to limit neurodegeneration and demyelination and promote repair. As current MS therapies mainly target the peripheral immune system, there is an unmet need for treatments that act on the nervous system to limit neurodegeneration and demyelination. Central to lesion maintenance is the scar tissue, mainly constituted by astrocytes.

Rationale and hypothesis

Astrocytes are the most abundant glia cell type of the CNS and are essential for tissue homeostasis, e.g. they provide metabolites and growth factors to neurons, participate in blood brain barrier maintenance and control immune cell trafficking and activation. Upon CNS injury they undergo morphological, molecular, and functional remodeling that may promote or dampen neuronal damage, demyelination and inflammation. Our lab has provided seminal descriptions about how these glia cells are reacting to several stimuli leading to complex networks of intracellular events within the scar in multiple sclerosis. On the other hand, distinct activation modes may share signaling steps and effector mechanisms, opening the way to the identification of central glial checkpoints amenable for therapeutic targeting. Our hypothesis is that checkpoints for CNS neuroinflammation exist and may be used to modulate CNS pathology.

Objectives and specific aims

The main objective is the identification of key signaling checkpoints in the astrocyte contributing to CNS neuroinflammation. The first specific aim is the identification of potential glial markers, regulators and processes associated with disease. Here, the analysis of available transcriptomics data relative to distinct compartments, including CNS, and to distinct types of CNS lesions and cells (ref.4), may lead to the description of checkpoints altered under disease for the astrocyte and other cell types in MS. The second specific aim regards the assessment of the contribution of the molecular checkpoint to key astrocyte functions for scar formation and tissue degeneration. Here, in vitro studies will evaluate whether genetic and/or pharmacological approaches targeting the checkpoint will affect processes such as glial proliferation, migration, production of inflammatory and toxic mediators, and eventually, the downstream impact on other cell types (e.g. neurons). Finally, the third specific aim will determine the role of the checkpoint on disease expression in relevant in vivo models.

Expected outcomes

Identification of potential glial checkpoints
Impact of checkpoints on cell function and cell-cell interaction.
Disease expression in experimental mouse models upon modulation of the checkpoint.

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

Advanced knowledge of Neurobiology, Immunology, Pathology, Molecular Biology, Histology, Transcriptomics, Bioinformatics.

Logical thinking, Scientific English.

References (max. 15)

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8. Massimo Acquaviva, Ramesh Menon, Marco Di Dario, Gloria Dalla Costa, Marzia Romeo, Francesca Sangalli, Bruno Colombo, Lucia Moiola, Vittorio Martinelli, Giancarlo Comi, Cinthia Farina. *Inferring Multiple Sclerosis stages from blood transcriptome via machine learning*. Cell Rep. Med. 1, 2020.
9. Martina Severa, Fabiana Rizzo, Sundararajan Srinivasan, Marco Di Dario, Elena Giacomini, Maria Chiara Buscarinu, Melania Cruciani, Marilena P. Etna, Silvia Sandini, Rosella Mechelli, Antonella Farina, Pankaj Trivedi, Paul J. Hertzog, Marco Salvetti, Cinthia Farina, Eliana M. Coccia. *A cell type-specific transcriptomic approach to map B cell and monocyte type I Interferon-linked pathogenic signatures in Multiple Sclerosis*. J. Autoimmunity 101: 1, 2019
10. Sundararajan Srinivasan, Marco Di Dario, Alessandra Russo, Ramesh Menon, Elena Brini, Marzia Romeo, Francesca Sangalli, Gloria Dalla Costa, Mariaemma Rodegher, Marta Radaelli, Lucia Moiola, Daniela Cantarella, Enzo Medico, Gianvito Martino, Roberto Furlan, Vittorio Martinelli, Giancarlo Comi, Cinthia Farina. *Dysregulation of multiple sclerosis risk genes and pathways at distinct stages of disease*. Neurology: Neuroimmunol. Neuroinflamm. 4 (3): e337, 2017.
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15. Emanuela Colombo, Chiara Cordiglieri, Giorgia Melli, Jia Newcombe, Markus Krumbholz, Luis Parada, Enzo Medico, Reinhard Hohlfeld, Edgar Meinl and Cinthia Farina. *Stimulation of the neurotrophin receptor TrkB on astrocytes drives nitric oxide production and neurodegeneration*. J.Exp. Med. 209, 2012.