**PROGETTO**

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| **Supervisore:** | Paola Panina |
| Titolo/*Title:* | Unveiling the role of short-chain fatty acids in neural homeostasis |
| *Curriculum:* | Medicina Molecolare – Neuroscienze e Neurologia Sperimentale |
| Link alla pagina personale del sito web di Ateneo o del polo ospedaliero di riferimento: | http://www.unisr.it/k-teacher/panina-paola/ |

**Descrizione del progetto (max 3.000 caratteri spazi inclusi)**

**Background/gap of knowledge** Recent studies show that gut microbiota strongly influences brain physiology and that alterations of its composition are present in many brain pathologies, including Multiple sclerosis (MS), although the mechanisms through which it modulates neuroinflammation and neurodegeneration are still poorly defined. The microbiota mediates its action principally through the synthesis of specific metabolites that act as messengers. These metabolites can modulate the immune and nervous systems, induce tissue repair, and promote stemness. Microbial metabolites of primary importance are the SCFAs (mainly acetate, propionate, an. butyrate), produced by the fermentation of dietary fiber. Levels of butyrate and propionate are altered in MS patients compared to healthy donors[1,2]. Supplementing SCFAs through the diet shows beneficial effects both in experimental autoimmune encephalomyelitis (EAE), a murine model of MS[3] and in patient-derived data[4], although the molecular mechanisms through which they act are still unclear and, paradoxically, no studies investigate their role in the nervous system in the frame of neuroinflammation. SCFAs produced and released in the colon have been shown to communicate directly with the enteric nervous system (ENS)[5] and to influence the stemness of intestinal stem cells and potentially also enteric neural stem cells[6].

**Rationale and hypothesis** The project is based on the hypothesis that SCFAs have the potential to modulate not only immunity but also the nervous system homeostasis and neural precursor cells (NPCs) stemness, which is extremely relevant in neuroinflammatory/neurodegenerative diseases like MS. The effects of SCFAs on the CNS may be mediated not only by the circulating SCFAs that cross the blood-brain barrier but also by the *in situ* activation of the ENS, which signals through the gut/brain axis.

**Objectives and specific aims.** The main objective of this project is to establish a mechanistic link between altered levels of SCFAs and neuroimmune alterations in MS, by showing how SCFAs act on the CNS via the ENS. The specific aims are:
1. understanding how SCFAs (a) stimulate neurogenesis of the enteric and central nervous system and (b) modulate enteric and central neuronal homeostasis by adapting the cellular response to a stressed environment.
2. investigating how SCFAs-stimulated enteric neurons signal through the gut/brain axis, contributing to the preservation of CNS homeostasis during neurodegeneration and neuroinflammation.

**Expected outcomes.** Preliminary data currently generated in the lab using *in vitro* human brain organoids indicate that SCFAs induce NPC differentiation into mature populations. We expect to validate this result also *in vivo* by taking advantage of the animal models described below. Given our preliminary data showing that SCFAs prevent oxidative stress in human neurons, we predict that they could have an overall beneficial effect on the EAE mouse model.

**Competenze che deve acquisire lo studente** (Max 600 caratteri spazi inclusi):

- Pose a research question;
- examine the range of modes of inquiry;
- identify the appropriate research mode and procedure, define a sample/population;
- identify a data collection strategy; analyze and interpret the data; draw conclusions from the data;
- animal models;
- write research reports/papers;
- present a scientific project to an internal and external audience.

**Bibliografia** (max. 15)

1. Zhou, X. et al. Gut microbiome of multiple sclerosis patients and paired household healthy controls reveal associations with disease risk and course. Cell 185, 3467-3486.e16 (2022).
2. Levi, I. et al. Potential role of indolelactate and butyrate in multiple sclerosis revealed by integrated microbiome-metabolome analysis. Cell Rep Med 2, 100246 (2021).
3. Mizuno, M., Noto, D., Kaga, N., Chiba, A. & Miyake, S. The dual role of short fatty acid chains in the pathogenesis of autoimmune disease models. PLoS One 12, (2017).
4. Duscha, A. et al. Propionic Acid Shapes the Multiple Sclerosis Disease Course by an Immunomodulatory Mechanism. Cell 180, 1067-1080.e16 (2020).
5. Jameson, K. G., Olson, C. A., Kazmi, S. A. & Hsiao, E. Y. Toward Understanding Microbiome-Neuronal Signaling. Molecular Cell vol. 78 Preprint at https://doi.org/10.1016/j.molcel.2020.03.006 (2020).
6. Yang, L. L. et al. Enteric short-chain fatty acids promote proliferation of human neural progenitor cells. J Neurochem (2019) doi:10.1111/jnc.14928.
7. Lagace, D. C. et al. Dynamic contribution of nestin-expressing stem cells to adult neurogenesis. Journal of Neuroscience 27, 12623–12629 (2007).
8. Frith, T. J. R. et al. Retinoic Acid Accelerates the Specification of Enteric Neural Progenitors from In-Vitro-Derived Neural Crest. Stem Cell Reports 15, (2020).
9. Loffet, E., Brossard, L. & Mahe, M. M. Pluripotent stem cell derived intestinal organoids with an enteric nervous system. in Methods in Cell Biology vol. 159 (2020).