PROGETTO

Supervisore:	Gianvito Martino
Titolo/*Title:*	Discovery of gene regulation programs in multiple sclerosis.
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/martino-gianvito/

Descrizione del progetto (max 3.000 caratteri spazi inclusi)

Background/gap of knowledge. Multiple sclerosis (MS) is a neuroinflammatory disease characterized by myelin and axonal damage, which represents the major cause of progressive neurological disability in young adults and has a large societal impact[1-4]. Familial clustering suggests that a hereditary factor is involved in determining the risk of MS[5]. However, a monozygotic twin whose co-twin has MS has only 25% risk of developing the disease[6], suggesting that epigenetic mechanisms mediate the response to many environmental influences that ultimately affect disease development[7]. Epigenetic regulatory patterns include chromatin modifications, remodeling, non-coding RNAs and DNA methylation[8]. Elements that participate in epigenetic regulation mainly adjust chromatin architecture or alter its accessibility to transcription factor (TF), influencing gene expression[9].

Rationale and hypothesis. The analysis of single cell transcriptome combined with single cell chromatin state assessment in MS-relevant cell types (NPCs, neurons, oligodendrocytes, microglia) of monozygotic (MZ) twin pairs clinically discordant for MS , will reveal novel regulatory programs associate with onset of MS pathology.

Objectives and specific aims. This project aims to analyze the single cell transcriptome combined with single cell chromatin state analysis to reveal heterogeneity in the regulatory landscape of cells, which can bias fate decision upstream of transcriptional changes. Validation of novel regulatory mechanisms will be performed by gene editing in human brain organoids.

Expected outcomes. A preliminary analysis on one MZ twin pair clinically discordant for MS revealed several differentially expressed genes. Enrichment analysis indicate that significantly up-regulated genes were associated with immune mediated-responses indicating different microglial cell programs in the MS versus the healthy twin. The analysis of 5 more twin pairs is expected to unravel the pathogenetic mechanisms of MS.

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;
- write research reports/papers;
- present a scientific project to an internal and external audience.

Bibliografia (max. 15)

1. Patrikios, P., *et al.* Remyelination is extensive in a subset of multiple sclerosis patients. *Brain* **129**, 3165 3172 (2006).
2. Skulina, C., *et al.* Multiple sclerosis: brain-infiltrating CD8+ T cells persist as clonal expansions in the cerebrospinal fluid and blood. *Proc Natl Acad Sci U S A* **101**, 2428-2433 (2004).
3. Nave, K.A. Myelination and the trophic support of long axons. *Nat Rev Neurosci* **11**, 275-283 (2010).
4. Hartung, D.M., Bourdette, D.N., Ahmed, S.M. & Whitham, R.H. The cost of multiple sclerosis drugs in the US and the pharmaceutical industry: Too big to fail? *Neurology* **84**, 2185-2192 (2015).
5. Sawcer S, Franklin RJ, Ban M. Multiple sclerosis genetics. *Lancet Neurol*. 2014;13(7):700-709. doi:10.1016/S1474-4422(14)70041-9
6. Westerlind H, Ramanujam R, Uvehag D, et al. Modest familial risks for multiple sclerosis: a registry-based study of the population of Sweden. *Brain*. 2014;137(Pt 3):770-778. doi:10.1093/brain/awt356
7. Olsson T, Barcellos LF, Alfredsson L. Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. *Nat Rev Neurol*. 2017;13(1):25-36. doi:10.1038/nrneurol.2016.187
8. Clapier CR, Cairns BR. 2009. The biology of chromatin remodeling complexes. Annu Rev Biochem 78:273–304.
9. Satpathy AT, Granja JM, Yost KE, et al. Massively parallel single-cell chromatin landscapes of human immune cell development and intratumoral T cell exhaustion. *Nat Biotechnol*. 2019;37(8):925-936. doi:10.1038/s41587-019-0206-z
10. Tedesco M, Giannese F et al Chromatin Velocity reveals epigenetic dynamics by single-cell profiling of heterochromatin and euchromatin. Nat Biotechnol. 2022 Feb;40(2):235-244. doi: 10.1038/s41587-021-01031-1. Epub 2021 Oct 11.PMID: 34635836