PROGETTO

Supervisore:	Colnaghi Luca
Titolo	Integrated multi-omic profiling of NEDAMSS: Uncovering the pathological consequences of a rare neurodevelopmental disorder
Curriculum:	Neuroscienze e Neurologia Sperimentale
Link alla pagina personale del sito web di Ateneo o del polo ospedaliero di riferimento:	https://research.hsr.it/en/divisions/neuroscience/luca-colnaghi.html

Descrizione del progetto (max 3.000 caratteri spazi inclusi)

Background/Lacune di conoscenza

Neurodevelopmental Disorder with Regression, Abnormal Movements, Loss of Speech, and Seizures (NEDAMSS) is a recently characterized, severe neurological condition caused by mutations in the IRF2BPL gene (1-4). Clinical presentation typically involves a period of normal early development followed by rapid regression, leading to the loss of motor and language milestones, dystonia, and refractory epilepsy. Despite its clinical recognition, the biological role of the encoded protein, IRF2BPL, remains poorly understood, hindering the development of targeted therapies. A significant portion of the protein consists of intrinsically disordered regions (IDRs). These domains are hallmark features of proteins capable of liquid-liquid phase separation (LLPS), a process that organizes cellular space into functional, membrane-less organelles (condensates). Our preliminary findings indicate that while wild-type IRF2BPL forms reversible, functional condensates, patient-derived mutations disrupt this biophysical balance, leading to aberrant cytosolic LLPS and the formation of toxic, insoluble protein aggregates. The transition from functional phase separation to irreversible aggregation is a shared theme in many neurodegenerative diseases (e.g., ALS, FTLD) (6-7). In NEDAMSS, this transition is thought to cause a loss-of-function of the protein's normal transcriptional and ubiquitin-ligase activities (5). Preliminary data from our group suggests that these alterations trigger widespread transcriptomic changes, particularly involving the WNT signaling pathway, yet how these molecular events specifically impact human neuronal maturation and homeostasis remains unknown (5). To untangle these complex interactions, a systems biology approach is required. Single-cell transcriptomics (scRNA-seq) of human iPSC-derived neurons allows for the dissection of cell-type-specific responses to IRF2BPL dysfunction, identifying which neuronal

subpopulations are most vulnerable. Simultaneously, Mass Spectrometry (MS) provides a map of the IRF2BPL interactome, revealing how mutations affect the protein's binding partners.

Razionale e ipotesi

We hypothesize that IRF2BPL mutations trigger a systemic remodeling of the neuronal proteome and transcriptome, driving the progressive regression observed in NEDAMSS.

Specifically, we propose that:

The mutant IRF2BPL interactome is depleted of functional partners and simultaneously enriched in proteins sequestered within aberrant cytoplasmic condensates.

By integrating scRNA-seq and MS-proteomics through systems biology modeling, we will identify specific molecular targets and pathways that can be modulated to bypass the IRF2BPL defect, with the ultimate goal of restoring neuronal homeostasis.

Obiettivi e finalità specifiche

Leveraging the *in-silico* expertise of the lab and wet lab reagents and tools (5), we will:

1. Characterize the differential IRF2BPL interactome through MS analysis.

2. Identify transcriptional signatures using scRNA-seq in iPSC-derived neurons.

3. Perform multi-omic integration and network medicine analysis (8) for therapeutic target identification.

Risultati attesi

The successful completion of this project will provide the first multi-omic characterization of NEDAMSS, moving the field from descriptive clinical observations to a mechanistic understanding of the disease. Furthermore, the identification of druggable targets will provide a solid foundation for drug repurposing or screening, offering hope for therapeutic intervention in this rare and devastating disorder currently without a cure.

Competenze che dovrà acquisire la/il Dottoranda/o(in inglese, max 600 caratteri spazi inclusi)

During the Ph.D., the student will be expected to progressively develop autonomy in designing, conducting, and interpreting computational workflows and experimental data. From a technical standpoint, the candidate will gain hands-on expertise in in silico analysis of both bulk and single-cell RNA sequencing datasets. Furthermore, the project will involve the processing and interpretation of mass spectrometry proteomics, culminating in the application of machine learning approaches for multi-omic integration. Bases of cell culture, asssited by other members

of the lab will also be provided. This comprehensive training will equip the student with a robust systems biology toolkit to tackle the complexities of neurodevelopmental disorders.

Bibliografia (massimo 15 voci)

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