PROGETTO-1

Supervisore: Ivan de Curtis

Titolo/*Title*: **Assembly and regulation of plasma membrane-associated platforms during tumor cell motility.**

Curriculum: Biologia Cellulare e Molecolare

Link alla pagina personale del sito web di Ateneo o del polo ospedaliero di riferimento: https://research.hsr.it/en/divisions/neuroscience/cell-adhesion.html

Descrizione del progetto (max 3.000 caratteri spazi inclusi)

Background/gap of knowledge

Biomolecular condensates (BCs) form by phase separation of proteins into membrane-less assemblies with liquid-like properties. BCs are important for the functional and dynamic organization of the intracellular space. Data from the lab have shown that the ERC1 protein guides the assembly of plasma membrane associated platforms (PMAPs) by phase separation (Sala et al, 2019; de Curtis, 2021). PMAPs include a protein network promoting cell migration and invasion (Ramella et al, 2022), by endorsing the turnover of adhesions and invadosomes (Astro and de Curtis, 2015; Sala et al, 2018).

Rationale and hypothesis

The mechanisms regulating the assembly/disassembly of ERC1-induced PMAPs are unknown. The aim of this PhD project is to investigate the mechanisms that regulate ERC1 phase separation and PMAPs formation, with the aim of identifying strategies to interfere with PMAPs function and tumor cell invasion.

Objectives and specific aims

Recent results from the lab support the involvement of specific phosphatases (Ripamonti et al, 2022) and kinases (Ramella et al, 2024) in the turnover of ERC1 condensates and PMAPs to regulate tumor cell motility and invasion. The PhD student will explore phosphorylation events specifically affecting PMAPs, turnover of adhesions, and the protrusive activity of cells during migration on extracellular matrix. Available kinase-dead mutants and specific inhibitors may be used to prove the requirement of phosphorylation for the turnover of PMAPs, while phosphorylation defective and phospho-mimetic mutants of the target proteins will be tested in a number of motility assays to look for effects on migration and invasion. The PhD candidate will have the opportunity to learn and combine several molecular cell biology approaches including high resolution imaging on living cells, biochemical approaches linked to phosphoproteomics, and functional cell motility assays.

Expected outcomes

The outcome from this project is expected to highlight fundamental new mechanisms regulating cell migration that may be extended to different cell types, and to provide new specific targets for cancer therapy.

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

The student will acquire skills in molecular cell biology approaches including *in vitro* and *in vivo* cell motility and invasion assays; confocal, FRAP, TIRF imaging on fixed and live cells; cell biochemistry and protein structure-function analysis.

Bibliografia (max. 15)

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2) Ripamonti M, Lamarca A, Davey NE, Tonoli D, Surini S, de Curtis I. (2022) A functional interaction between liprin-α1 and B56γ regulatory subunit of protein phosphatase 2A supports tumor cell motility. Commun Biol. 5:1025.
3) Ramella M, Ribolla LM, de Curtis I. Liquid-Liquid Phase Separation at the Plasma Membrane-Cytosol Interface: Common Players in Adhesion, Motility, and Synaptic Function. J Mol Biol. (2022) 434:167228.
4) Ripamonti M, Wehrle-Haller B, de Curtis I. Paxillin: A Hub for Mechano-Transduction from the β3 Integrin-Talin-Kindlin Axis. Front Cell Dev Biol. (2022) 10:852016.
5) de Curtis I. Biomolecular Condensates at the Front: Cell Migration Meets Phase Separation. Trends Cell Biol. (2021) 3:145-148.
6) Pehkonen H, de Curtis I, Monni O. Liprins in oncogenic signaling and cancer cell adhesion. Oncogene. (2021) 40:6406-6416.
7) Sala K et al. 2019. The ERC1 scaffold protein implicated in cell motility drives the assembly of a liquid phase. Sci Rep. 9:13530
8) Sala K et al. 2018. Identification of a membrane-less compartment regulating invadosome function and motility. Sci Rep. 8:1164.
9) Astro V et al, 2016. Liprin-α1 and ERC1 control cell edge dynamics by promoting focal adhesion turnover. Sci Rep. 6:33653.
10) Astro V, de Curtis I. 2015. Plasma membrane-associated platforms: dynamic scaffolds that organize membrane-associated events. Science Signal. 8:re1.