Molecular Medicine - Basic and Applied Immunology and Oncology

Ivan de Curtis Lab: https://research.hsr.it/en/divisions/neuroscience/cell-adhesion.html

Mechanisms of regulation of a molecular network promoting cell invasion.

We have identified a molecular network including the proteins liprin-α1, ERC and LL5 that are essential for cell migration and invasion. These proteins interact with each other to form plasma membrane associated platforms (PMAPs), dynamic membrane-less structures that promote protrusion at the cell edge. Interestingly, PMAPs are dynamically associated to focal adhesions at the front of migrating tumor cells, affecting their turnover (*de Curtis, 2021; Astro et al, 2016*). PMAPs also promote invadosome-mediated extracellular matrix degradation, which is required for tumor cell invasion (*Sala et al, 2018*). Depletion of the protein complex inhibits the turnover of adhesions. Aim of this PhD project is to explore the mechanisms that regulate the function of PMAPs during cell migration and invasion. Recent data from the lab support the hypothesis that PMAPs are formed by phase separation of ERC1 that forms biomolecular condensates at specific sites within migrating tumor cells (*Sala et al, 2019*). This project will address the mechanisms that drive the assembly and turnover of PMAPs at specific sites of the migrating tumor cells. Specific protein kinases and protein phosphatases have been recently identified in the lab as likely regulators of PMAP assembly and function. The PhD student will investigate how these regulatory enzymes affect the assembly and disassembly of PMAPs, and the consequences of perturbing PMAPs dynamics on tumor cell invasion. The combination of established functional assays with high resolution time-lapse imaging by confocal microscopy will be used to study the effects of kinases and phosphatases on PMAPs organization and on the migration and extracellular matrix degradation by invasive tumor cells. Proteomics and phosphoproteomics will be applied to identify candidate proteins implicated in the protrusive activity required for cell motility and invasion. Interesting candidates will be tested for their role *in vivo*, by using invasive tumor cell lines with silenced/mutated protein, to address the effects on the development of tumors and metastases. Results will highlight new mechanisms influencing the invasive behavior of malignant cells, and may potentially reveal new targets for therapy.

Skills to be acquired by the student:

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.

de Curtis 2021. Biomolecular Condensates at the Front: Cell Migration Meets Phase Separation. *Trends Cell Biol. 31:145-148.*

Sala K et al. 2019. The ERC1 scaffold protein implicated in cell motility drives the assembly of a liquid phase. *Sci Rep.* 9:13530

Sala K et al. 2018. Identification of a membrane-less compartment regulating invadosome function and motility. *Sci Rep. 8:1164.*

Astro V et al, 2016. Liprin-α1 and ERC1 control cell edge dynamics by promoting focal adhesion turnover. *Sci Rep. 6:33653.*

Astro V, de Curtis I. 2015. Plasma membrane-associated platforms: dynamic scaffolds that organize membrane-associated events. *Science Signal. 8:re1.*

Astro V et al, 2014. Liprin-α1, ERC1 and LL5 define polarized and dynamic structures that are implicated in cell migration. *J Cell Sci. 127:3862-76.*