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Soutenance de thèse

The role of the Cdc42-specific guanine nucleotide exchange factor Fgd1 in tumor cell invasion.

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In vitro, degradation of the extracellular matrix (ECM) by invasive tumor cells is carried out by invadopodia, proteolytically active protrusions emanating from the ventral membrane of cells cultured on two dimensional ECM substrates. Identification and characterization of novel molecular components of the invadopodia machinery is now witnessing a relevant interest. The guanine nucleotide exchange factors (GEFs) Fgd1, a specific GEF for Cdc42, has been recently brought into the picture of invadopodia components and regulators. Notwithstanding, how Fgd1 is regulated in invasive cancer cells remains poorly understood. My project aimed to further elucidate Fgd1 regulation in cancer cells. I showed that the cellular distribution of endogenous Fgd1 quantitatively changes along the different stages of invadopodia formation, and that Fgd1 accumulates at invadopodia sites concomitantly with the initial assembling of the actin/cortactin core. The N-terminal proline rich domain (PRD) of Fgd1 is essential for its localization and function at invadopodia. Furthermore, using a yeast two hybrid approach, Filamin A (FLNa) was identified as a novel Fgd1 binding partner and this interaction was validated *in vivo*. I report that FLNa co-localizes with Fgd1 at invadopodia and is required for their formation and function. I hypothesized that FLNa may be involved in the SCF FWD1/β-TrCP –mediated proteasome degradation of Fgd1, a process that is strictly connected to the Cdc42 activation rate. In my model, FLNa may act as a scaffold to connect Fgd1 and Cdc42 for local activation of the small GTPase, and to increase Fgd1 stability by preventing its proteasomal degradation. Taken together, my findings provide novel insights on the role of Fgd1 in invadopodia biogenesis.

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