
BIOGRAPHICAL SKETCH

NAME: de Curtis, Ivan

POSITION TITLE: Full Professor of Cell Biology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date MM/YYYY	FIELD OF STUDY
University of Milano	Laurea	05/1979	Biology
University of Milano	PHD	12/1987	Molecular Cell Biology
European Molecular Biology Laboratory	Postdoctoral	09/1988	Molecular Cell Biology
University of California, San Francisco	Postdoctoral	03/1992	Molecular & Cellular Neuroscience

A. Personal Statement

My laboratory has used biochemistry and molecular cell biology to explore the mechanisms regulating cell motility, recently supported by collaborations aimed at addressing structure-function relationships of the molecular players under study (Prof. Roberta Pierattelli for NMR; Prof. Davide Mazza for single molecule analysis). Our studies have contributed to the analysis of the functions of Rac GTPases in cultured primary neurons and in mice models *in vivo*. I am committed to the training and development of young researchers, mostly joining my lab at the beginning of their career in science.

We have performed extensive work on the role of Rac GTPases and functionally associated networks regulating cell motility and neuronal development. We have addressed the function of ERC1/Liprin- α 1 networks in cell motility and invasion, with important implications for pathology. We started by considering the very poorly explored function of Liprin- α 1/ERC1 in tumor cells, continuing by discovering that these scaffolds are part of a dynamic network that is necessary for the efficient motility of tumor and non-tumor cells. Our results have contributed to open up a new pathway for the study of this protein complex in a setting different from the presynaptic terminal, where Liprin- α and associated proteins have been analyzed for several years.

Several years ago we have identified Rac3/Rac1B as a neural-specific Rac GTPase, and developed the idea that Rac3 is essential for the normal development of the vertebrate brain. With our studies in cultured neurons and animal models, we have proposed and supported with experimental evidence the concept that two Rac GTPases are needed for the development of a normal mammalian brain. Recent genetic studies have identified mutations of the *Rac3* gene in human patients developing intellectual disabilities.

I am full professor since 2007, with extensive experience in teaching undergraduate (Molecular Cell Biology and Biochemistry) and graduate students at the San Raffaele Vita-Salute University. Since I started my lab in 1992 at the San Raffaele Institute/Vita-Salute San Raffaele University, I have been supervising the research projects of post-master junior research fellows (≈ 25), PhD students (≈ 10), and postdocs (13), as well as several undergraduate Biology/Biotechnology students preparing their experimental Master thesis in my lab.

Ongoing projects include:

AIRC - IG 29097 (de Curtis, PI)

Mechanisms of assembly and regulation of liprin-associated platforms during tumor cell invasion.
(2/1/2024–1/1/2029)

Telethon-Cariplo - RI0298 (de Curtis, PI)

Structure-function characterization of TANC2, a novel postsynaptic candidate associated to neuropsychiatric disorders.
(1/7/2023–30/6/2025)

MUR-PRIN - 2022EMZJL4 (de Curtis, PI and Coordinator)

Supramolecular assemblies in cell invasion as targets for cancer therapy.
(28.9.23–27.9.25)

CanServ / Instruct-ERIC - PID 29376 (de Curtis, PI)

Characterization by NMR of ERC1 homotypic and heterotypic interactions implicated in tumor cell invasion
(2024/2025)

B. Positions, Scientific Appointments, and Honors

2007– Present	Full Professor, School of Medicine, San Raffaele Vita-Salute University (UniSR), Milano
1992 – Present	Group leader, San Raffaele Scientific Institute, Milano
2011 – present	Coordinator of the curriculum in Cellular Molecular Biology, PhD Course in Molecular Medicine, UniSR
2018–2022	Member of reviewing panel of the Priority Program “Molecular mechanisms of functional phase separation” (SPP 2191/1 and 2), Deutsche Forschungsgemeinschaft
2019 – present	Reviewing Editor, Frontiers in Cellular Neuroscience
2011 – present	Academic Editor, PlosOne
2006 – 2012	Associate Editor, Biology of the Cell
1998 – present	Member of The American Society for Cell Biology

Ad-hoc reviewer for several international journals (Science, Nature, Molecular Psychiatry, Journal of Neuroscience, EMBO Journal, Journal of Cell Biology) and granting agencies (ERC Advanced Grant, MRC–Medical Research Council, ANR–Agence Nationale de la Recherche, Swiss Cancer League)

C. Contributions to Science

Following on our identification of the Rac3/Rac1B GTPase as a novel member of the Rac family, by using a combination of morphological and physiological methods in *in vivo* mice models, we have shown that the effects of Rac on the development of GABAergic interneurons are mediated by the combined action of the ubiquitous Rac1 and the neural-specific Rac3 GTPases. The two GTPases have also distinct effects on the morphology of the dendritic spines in excitatory neurons.

Vaghi V, Pennucci R, Talpo F, Corbetta S, Montinaro V, Barone C, Croci L, Spaiardi P, Consalez GG, Biella G, **de Curtis I.** (2014) Rac1 and Rac3 GTPases control synergistically the development of cortical and hippocampal GABAergic interneurons. *Cereb Cortex.* 24:1247-58.

Pennucci R, Talpo F, Astro V, Montinaro V, Morè L, Corsi M, Castoldi V, Chiaretti S, Bianchi V, Marenga S, Cambiaghi M, Tonoli D, Leocani L, Biella G, D'Adamo P, **de Curtis I.** (2016) Loss of Either Rac1 or Rac3 GTPase Differentially Affects the Behavior of Mutant Mice and the Development of Functional GABAergic Networks. *Cereb Cortex.* 26:873-890.

Pennucci R, Gucciardi I, **de Curtis I.** (2019) Rac1 and Rac3 GTPases differently influence the morphological maturation of dendritic spines in hippocampal neurons. *PLoS One.* 14(8):e0220496.

By pull-down with active GTP-bound Rac1/Rac3 GTPases and mass spectrometry, we have identified the Rac-interacting signaling and scaffolding complex PAK/PIX/GIT1 (at the time called by us p95-APP1). Given the participation of Arf proteins in regulating membrane traffic, we proposed that the ArfGAPs act as molecular devices to coordinate membrane traffic and cytoskeletal reorganization during cell motility. From there, our later studies have extended the identification and characterization of a regulatory network that includes the Liprin- α 1/ERC1/LL5 functional complex relevant for cell motility and invasion, currently under study in the lab.

Di Cesare A, Paris S, Albertinazzi C, Dariozzi S, Andersen J, Mann M, Longhi R, **de Curtis I.** (2000) p95-APP1 links membrane transport to Rac-mediated reorganization of actin. *Nat Cell Biol.* 2:521-530.

Earlier studies had characterized Liprin-a proteins mainly as synaptic regulators. We have discovered a role of Liprin- α 1 in promoting the motility of non-neuronal cells, opening a new area of research for the role of this protein in cell motility. We found that Liprin- α 1 is important for the regulation of cell edge dynamics, and that Liprin- α 1 and a number of associated proteins are interesting players in the regulation of cell adhesion and motility, with an important role as regulators of tumor cell invasion. Through the analysis of the effects of Liprin- α 1 silencing or overexpression *in vivo*, we have discovered the importance of this protein in the formation of metastases in mice, and the distinct effects of different Liprin family members in tumor cell motility and invasion in culture.

Asperti C, Astro V, Totaro A, Paris S, **de Curtis I.** (2009) Liprin- α 1 promotes cell spreading on the extracellular matrix by affecting the distribution of activated integrins. *J Cell Sci.* 122:3225-3232.

Astro V, Asperti C, Cangi MG, Doglioni C, **de Curtis I.** (2011) Liprin- α 1 regulates breast cancer cell invasion by affecting cell motility, invadopodia and extracellular matrix degradation. *Oncogene* 30:1841-1849.

Chiaretti S, Astro V, Chiricozzi E, **de Curtis I.** (2016) Effects of the scaffold proteins liprin- α 1, β 1 and β 2 on invasion by breast cancer cells. *Biol Cell.* 108:65-75.

We have provided the first evidence for ERC1 assembling liquid-like biomolecular condensates that recruit PMAP components by specific protein-protein interaction.

Sala K, Corbetta A, Minici C, Tonoli D, Murray DH, Cammarota E, Ribolla L, Ramella M, Fesce R, Mazza D, Degano M, **de Curtis I.** (2019) The ERC1 scaffold protein implicated in cell motility drives the assembly of a liquid phase. *Sci Rep.* 9:13530.

By combining the effects of silencing endogenous proteins with time-lapse imaging in tumor cells with endogenous levels of tagged proteins, we discovered that the Liprin- α 1, ERC1 and LL5 scaffold proteins form specific dynamic networks at the protruding front of migrating cells. The three proteins regulate cell edge extension and the trafficking of integrins. Based on studies including ours, we have proposed a model for the assembly of PMAPs (plasma membrane-associated platforms), that is relevant for cell motility, but also for the assembly of the presynaptic terminals and for invadosome function. Recent evidence supports the formation of different PMAPs by liquid-liquid phase separation driven by ERC1. Our unpublished data show the formation of reversible liquid-like condensates forming *in vitro* with a purified fragment of ERC1 including the amino-terminal disordered region and two short coiled-coils. The functional characterization of PMAPs has allowed to discover some of the molecular mechanisms underlying the effects on cell edge protrusion and on the turnover of focal adhesions.

Astro V, Tonoli D, Chiaretti S, Badanai S, Sala K, Zerial M, **de Curtis I.** (2016) Liprin- α 1 and ERC1 control cell edge dynamics by promoting focal adhesion turnover. *Sci Rep.* 6:33653.

Astro V, Chiaretti S, Magistrati E, Fivaz M, **de Curtis I.** (2014) Liprin- α 1, ERC1 and LL5 define polarized and dynamic structures that are implicated in cell migration. *J Cell Sci.* 127:3862-76.

Astro V, **de Curtis I.** (2015) Plasma membrane-associated platforms: dynamic scaffolds that organize membrane-associated events. *Sci Signal.* 8(367):re1.

We have identified the Ser/Thr protein kinase DYRK3 and a regulatory subunit of protein phosphatase 2A as regulators of tumor cell motility, affecting PMAPs formation and cell edge dynamics.

Ripamonti M, Lamarca A, Davey NE, Tonoli D, Surini S, **de Curtis I.** (2022) A functional interaction between liprin- α 1 and B56 γ regulatory subunit of protein phosphatase 2A supports tumor cell motility. *Commun Biol.* 5:1025.

Ramella M, Ribolla LM, Surini S, Sala K, Tonoli D, Cioni JM, Rai AK, Pelkmans L, **de Curtis I.** 2024. Dual specificity kinase DYRK3 regulates cell migration by influencing the stability of protrusions. *iScience.* 27:109440.

Published Work in PubMed:

<https://pubmed.ncbi.nlm.nih.gov/?term=de+curtis+i&sort=date&size=200>