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Our team is interested in the molecular mechanisms underlying the appearance, survival and proliferation of cancer cells, and their dissemination. More specifically, by studying signalling networks, we aim to identify novel cellular targets with the therapeutic potential of differentiating between normal and cancer cells.

One of the most frequently mutated gene products in human cancers is the Ras protein. Its constitutive activation causes a cascade of intracellular signals whose components required for cancerous transformation has long been debated. The less studied among these cascades are the so-named “Ral driven signalling networks”, mobilized downstream of Ras by another GTPase, Ral, as shown both in experimental oncology and in human cancers. The activity of our team is organized around the question of the role of the Ral GTPase in oncogenic transformation and in physiological homeostasis.

The Ral GTPases have progressed from a status of molecular curiosity, appearing in evolution with metazoans and subsequently conserved in *Homo sapiens,* to the status of key player in oncogenesis. Ral exists neither in plants, nor in single-cell organisms. It is an essential link for the hyper signalling driven by oncogenic deregulated receptors or Ras mutants. Even better: cancer cells appear to be extremely susceptible to a drop in Ral activity, as this leads to their death.

We followed two parallel approaches relying on the known functional and physical conservation of the Ral signalling pathways between flies and mammals. We used Drosophila as a model organism for our genetic approach. We use biochemistry and cell biology techniques on vertebrate cells harbouring defined properties of “normal” or transformed cells for our cellular approach. Presently our efforts are exerted along two lines: the stamp collector approach and the hypothesis driven approach.

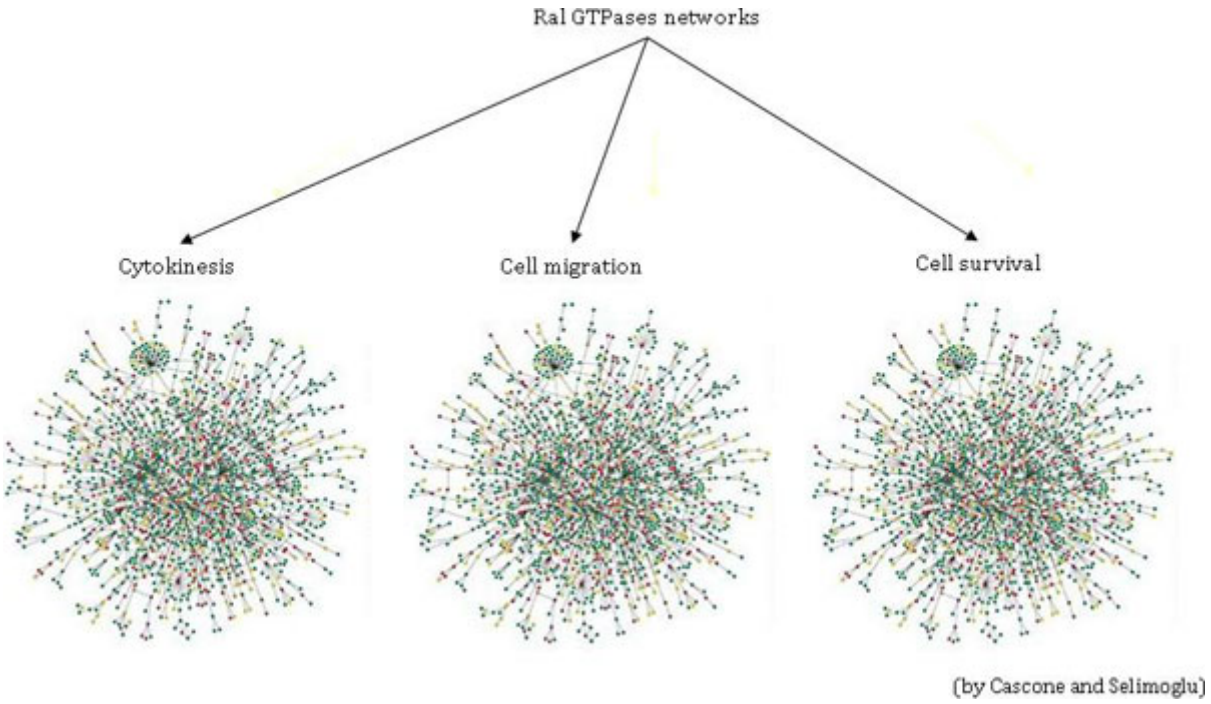

Figure 1 : Exploring the plasticity of the Ral networks. In various cellular "normal" or transformed human cell lines (HeLa, HBEC, RPE1), we are determining the impact of potentiel Ral interactomers, depleted by siRNA, on Ral-dependent phentoypes. The Ral interactome was defined by systematic Y2H screenings with all human and drosophila Ral GTPases, proteins of the exocyst complex, other direct and indirect partners of Ral (some determined during the course of the Drosoman screening projet).

We were able to identify proteins organized in networks (figure 1) and involved in oncogenic Ras transduction routes. We have achieved this by a molecular approach via the Drosoman screening project aimed at defining the protein-protein interaction map of more than 150 proteins of critical importance to oncogenesis or to cell life. A genetic screen in Drosophila has completed this data set: starting from cell death caused by a Ral mutation, we have identified a number of genes that either exacerbate the death rate, or conversely prevent death. Our aim is now to define the properties of these gene/protein partnerships. To do so, we are using a combination of cell biology, molecular biology, biochemistry and fly genetics methods together with High Content Screening approaches by automated cell imaging (The Biophenics platform).

After spending some time in deciphering Ral contribution to cytokinesis (figure 2) two main biological functions are phagocyting our efforts: 1) autophagy, where Ral GTP ases appear to be required and instructive, and the relationship of which to oncogenesis remains to be clarified both for at basic understanding and for pharmacological purposes, 2) anoikis : a remarkable and specific capacity of cancer cells to dodge death upon extra-cellular matrix detachment (notice that the corresponding in vitro assay -colony growth in soft agar- is a not so bad surrogate assay for tumorigenesis).

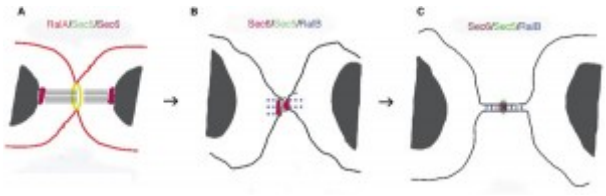

Figure 2: Spatial and temporal organization of Ral proteins and the exocyst during cytokinesis: a schematic.

Key publications

Year of publication 2014

Sylvain Lefort, Carine Joffre, Yann Kieffer, Anne-Marie Givel, Brigitte Bourachot, Giulia Zago, Ivan Bieche, Thierry Dubois, Didier Meseure, Anne Vincent-Salomon, Jacques Camonis, Fatima Mechta-Grigoriou (2014 Nov 27)
Inhibition of autophagy as a new means of improving chemotherapy efficiency in high-LC3B triple-negative breast cancers.
Autophagy : 2122-42 : DOI : 10.4161/15548627.2014.981788

Year of publication 2013

Sardar Faisal Mahmood, Nadège Gruel, Elodie Chapeaublanc, Aurianne Lescure, Thouis Jones, Fabien Reyal, Anne Vincent-Salomon, Virginie Raynal, Gaëlle Pierron, Franck Perez, Jacques Camonis, Elaine Del Nery, Olivier Delattre, François Radvanyi, Isabelle Bernard-Pierrot (2013 Oct 22)
A siRNA screen identifies RAD21, EIF3H, CHRAC1 and TANC2 as driver genes within the 8q23, 8q24.3 and 17q23 amplicons in breast cancer with effects on cell growth, survival and transformation.
Carcinogenesis : 670-82 : DOI : 10.1093/carcin/bgt351

Year of publication 2010

Maria Carla Parrini, Amel Sadou-Dubourgnoux, Kazuhiro Aoki, Katsuyuki Kunida, Marco Biondini, Anastassia Hatzoglou, Patrick Poullet, Etienne Formstecher, Charles Yeaman, Michiyuki Matsuda, Carine Rossé, Jacques Camonis (2010 May 14)
SH3BP1, an exocyst-associated RhoGAP, inactivates Rac1 at the front to drive cell motility.
Molecular cell : 650-61 : DOI : 10.1016/j.molcel.2011.03.032

Year of publication 2009

Carine Rosse, Etienne Formstecher, Katrina Boeckeler, Yingming Zhao, Joachim Kremerskothen, Michael D White, Jacques H Camonis, Peter J Parker (2009 May 22)
An aPKC-exocyst complex controls paxillin phosphorylation and migration through localised JNK1 activation.
PLoS biology : e1000235 : DOI : 10.1371/journal.pbio.1000235

Year of publication 2006

Maria Balakireva, Carine Rossé, Johanna Langevin, Yu-chen Chien, Michel Gho, Geneviève Gonzy-Treboul, Stéphanie Voegeling-Lemaire, Sandra Aresta, Jean-Antoine Lepesant, Yohanns Bellaiche, Michael White, Jacques Camonis (2006 Sep 25)
The Ral/exocyst effector complex counters c-Jun N-terminal kinase-dependent apoptosis in Drosophila melanogaster.
Molecular and cellular biology : 8953-63

Yuchen Chien, Sungchan Kim, Ron Bumeister, Yueh-Ming Loo, Sung Won Kwon, Cynthia L Johnson, Mirey G Balakireva, Yves Romeo, Levy Kopelovich, Michael Gale, Charles Yeaman, Jacques H Camonis, Yingming Zhao, Michael A White (2006 Feb 21)
RalB GTPase-mediated activation of the IkappaB family kinase TBK1 couples innate immune signaling to tumor cell survival.
Cell : 157-70