Year of publication 2015

María Elena Fernández-Sánchez, Sandrine Barbier, Joanne Whitehead, Gaëlle Béalle, Aude Michel, Heldmuth Latorre-Ossa, Colette Rey, Laura Fouassier, Audrey Claperon, Laura Brullé, Elodie Girard, Nicolas Servant, Thomas Rio-Frio, Hélène Marie, Sylviane Lesieur, Chantal Housset, Jean-Luc Gennisson, Mickaël Tanter, Christine Ménager, Silvia Fre, Sylvie Robine, Emmanuel Farge (2015 Jul 2)

Mechanical induction of the tumorigenic β-catenin pathway by tumour growth pressure.

Nature : 92-5 : DOI : 10.1038/nature14329

Summary

The tumour microenvironment may contribute to tumorigenesis owing to mechanical forces such as fibrotic stiffness or mechanical pressure caused by the expansion of hyper-proliferative cells. Here we explore the contribution of the mechanical pressure exerted by tumour growth onto non-tumorous adjacent epithelium. In the early stage of mouse colon tumour development in the Notch(+)Apc(+/1638N) mouse model, we observed mechanistic pressure stress in the non-tumorous epithelial cells caused by hyper-proliferative adjacent crypts overexpressing active Notch, which is associated with increased Ret and β-catenin signalling. We thus developed a method that allows the delivery of a defined mechanical pressure in vivo, by subcutaneously inserting a magnet close to the mouse colon. The implanted magnet generated a magnetic force on ultra-magnetic liposomes, stabilized in the mesenchymal cells of the connective tissue surrounding colonic crypts after intravenous injection. The magnetically induced pressure quantitatively mimicked the endogenous early tumour growth stress in the order of 1,200 Pa, without affecting tissue stiffness, as monitored by ultrasound strain imaging and shear wave elastography. The exertion of pressure mimicking that of tumour growth led to rapid Ret activation and downstream phosphorylation of β-catenin on Tyr654, imparing its interaction with the E-cadherin in adherens junctions, and which was followed by β-catenin nuclear translocation after 15 days. As a consequence, increased expression of β-catenin-target genes was observed at 1 month, together with crypt enlargement accompanying the formation of early tumorous aberrant crypt foci. Mechanical activation of the tumorigenic β-catenin pathway suggests unexplored modes of tumour propagation based on mechanical signalling pathways in healthy epithelial cells surrounding the tumour, which may contribute to tumour heterogeneity.

Angela Bellini, Virginie Bernard, Quentin Leroy, Thomas Rio Frio, Gaelle Pierron, Valérie Combaret, Eve Lapouble, Nathalie Clement, Herve Rubie, Estelle Thebaud, Pascal Chastagner, Anne Sophie Defachelles, Christophe Bergeron, Nimrod Buchbinder, Sophie Taque, Anne Auvrignon, Dominique Valteau-Couanet, Jean Michon, Isabelle Janoueix-Lerosey, Olivier Delattre, Gudrun Schleiermacher (2015 Feb 20)

Deep Sequencing Reveals Occurrence of Subclonal ALK Mutations in Neuroblastoma at Diagnosis.

Clinical cancer research : an official journal of the American Association for Cancer Research :

4913-21 : DOI : 10.1158/1078-0432.CCR-15-0423

Summary

In neuroblastoma, activating ALK receptor tyrosine kinase point mutations play a major role in oncogenesis. We explored the potential occurrence of ALK mutations at a subclonal level using targeted deep sequencing.

Thomas F Eleveld, Derek A Oldridge, Virginie Bernard, Jan Koster, Leo Colmet Daage, Sharon J Diskin, Linda Schild, Nadia Bessoltane Bentahar, Angela Bellini, Mathieu Chicard, Eve Lapouble, Valérie Combaret, Patricia Legoix-Né, Jean Michon, Trevor J Pugh, Lori S Hart, JulieAnn Rader, Edward F Attiyeh, Jun S Wei, Shile Zhang, Arlene Naranjo, Julie M Gastier-Foster, Michael D Hogarty, Shahab Asgharzadeh, Malcolm A Smith, Jaime M Guidry Auvil, Thomas B K Watkins, Danny A Zwijnenburg, Marli E Ebus, Peter van Sluis, Anne Hakkert, Esther van Wezel, C Ellen van der Schoot, Ellen M Westerhout, Johannes H Schulte, Godelieve A Tytgat, M Emmy M Dolman, Isabelle Janoueix-Lerosey, Daniela S Gerhard, Huib N Caron, Olivier Delattre, Javed Khan, Rogier Versteeg, Gudrun Schleiermacher, Jan J Molenaar, John M Maris (2015 Jan 15)
Relapsed neuroblastomas show frequent RAS-MAPK pathway mutations.
Nature genetics : 864-71 : DOI : 10.1038/ng.3333

Summary

The majority of patients with neuroblastoma have tumors that initially respond to chemotherapy, but a large proportion will experience therapy-resistant relapses. The molecular basis of this aggressive phenotype is unknown. Whole-genome sequencing of 23 paired diagnostic and relapse neuroblastomas showed clonal evolution from the diagnostic tumor, with a median of 29 somatic mutations unique to the relapse sample. Eighteen of the 23 relapse tumors (78%) showed mutations predicted to activate the RAS-MAPK pathway. Seven of these events were detected only in the relapse tumor, whereas the others showed clonal enrichment. In neuroblastoma cell lines, we also detected a high frequency of activating mutations in the RAS-MAPK pathway (11/18; 61%), and these lesions predicted sensitivity to MEK inhibition in vitro and in vivo. Our findings provide a rationale for genetic characterization of relapse neuroblastomas and show that RAS-MAPK pathway mutations may function as a biomarker for new therapeutic approaches to refractory disease.

Year of publication 2014

Ronald Lebofsky, Charles Decraene, Virginie Bernard, Maud Kamal, Anthony Blin, Quentin Leroy, Thomas Rio Frio, Gaëlle Pierron, Céline Callens, Ivan Bieche, Adrien Saliou, Jordan Madic, Etienne Rouleau, François-Clément Bidard, Olivier Lantz, Marc-Henri Stern, Christophe Le Tourneau, Jean-Yves Pierga (2014 Aug 14)

Circulating tumor DNA as a non-invasive substitute to metastasis biopsy for tumor genotyping and personalized medicine in a prospective trial across all tumor types.

Molecular oncology : 783-90 : DOI : 10.1016/j.molonc.2014.12.003

Summary

Cell-free tumor DNA (ctDNA) has the potential to enable non-invasive diagnostic tests for personalized medicine in providing similar molecular information as that derived from invasive tumor biopsies. The histology-independent phase II SHIVA trial matches patients with targeted therapeutics based on previous screening of multiple somatic mutations using metastatic biopsies. To evaluate the utility of ctDNA in this trial, as an ancillary study we performed de novo detection of somatic mutations using plasma DNA compared to metastasis biopsies in 34 patients covering 18 different tumor types, scanning 46 genes and more than 6800 COSMIC mutations with a multiplexed next-generation sequencing panel. In 27 patients, 28 of 29 mutations identified in metastasis biopsies (97%) were detected in matched ctDNA. Among these 27 patients, one additional mutation was found in ctDNA only. In the seven other patients, mutation detection from metastasis biopsy failed due to inadequate biopsy material, but was successful in all plasma DNA samples providing three more potential actionable mutations. These results suggest that ctDNA analysis is a potential alternative and/or replacement to analyses using costly, harmful and lengthy tissue biopsies of metastasis, irrespective of cancer type and metastatic site, for multiplexed mutation detection in selecting personalized therapies based on the patient's tumor genetic content.