Year of publication 2018

François Lallemand, Ambre Petitalot, Sophie Vacher, Leanne de Koning, Karim Taouis, Bernard S Lopez, Sophie Zinn-Justin, Nicole Dalla-Venezia, Walid Chemlali, Anne Schnitzler, Rosette Lidereau, Ivan Bieche, Sandrine M Caputo (2018 Feb 28)

Involvement of the FOXO6 transcriptional factor in breast carcinogenesis.

Oncotarget : 7464-7475 : DOI : 10.18632/oncotarget.23779

Summary

In mammals, FOXO transcriptional factors form a family of four members (FOXO1, 3, 4, and 6) involved in the modulation proliferation, apoptosis, and carcinogenesis. The role of the FOXO family in breast cancer remains poorly elucidated. According to the cellular context and the stage of the disease, FOXOs can have opposite effects on carcinogenesis. To study the role of FOXOs in breast carcinogenesis in more detail, we examined their expression in normal tissues, breast cell lines, and a large series of breast tumours of human origin. We found a very low physiological level of expression in normal adult tissues and high levels of expression in foetal brain. gene expressions fluctuate specifically in breast cancer cells compared to normal cells, suggesting that these genes may have different roles in breast carcinogenesis. For the first time, we have shown that, among the various genes, only was frequently highly overexpressed in breast cell lines and tumours. We also found that inhibition of the endogenous expression of FOXO6 by a specific siRNA inhibited the growth of the human breast cell lines MDA-MB-468 and HCC-38. FACS and Western blot analysis showed that inhibition of endogenous expression of FOXO6 induced accumulation of cells in G0/G1 phase of the cell cycle, but not apoptosis. These results tend to demonstrate that the overexpression of the human gene that we highlighted in the breast tumors stimulates breast carcinogenesis by activating breast cancer cell proliferation.

Year of publication 2017

Astrid Lièvre, Bérèngere Ouine, Jim Canet, Aurélie Cartier, Yael Amar, Wulfran Cacheux, Odette Mariani, Rosine Guimbaud, Janick Selves, Thierry Lecomte, Serge Guyetant, Ivan Bieche, Frédérique Berger, Leanne de Koning (2017 Oct 13)

Protein biomarkers predictive for response to anti-EGFR treatment in RAS wild-type metastatic colorectal carcinoma.

British journal of cancer : 1819-1827 : DOI : 10.1038/bjc.2017.353

Summary

Metastatic colorectal cancer (mCRC) patients with mutant KRAS or NRAS are ineligible for anti-epidermal growth factor receptor (anti-EGFR) therapy, as RAS mutations activate downstream pathways independently of EGFR and induce primary resistance. However, even among RAS wild-type (WT) patients, only a fraction responds to anti-EGFR therapy, suggesting that other mechanisms of resistance exist. We hypothesise that different (epi)genetic alterations can lead to primary anti-EGFR resistance and that the crucial end

point is the activation of protein signalling pathways.

Yann Neuzillet, Elodie Chapeaublanc, Clémentine Krucker, Leanne De Koning, Thierry Lebret, François Radvanyi, Isabelle Bernard-Pierrot (2017 Sep 9)
IGF1R activation and the in vitro antiproliferative efficacy of IGF1R inhibitor are inversely correlated with IGFBP5 expression in bladder cancer.
BMC cancer : 636 : DOI : 10.1186/s12885-017-3618-5

Summary

The insulin growth factor (IGF) pathway has been proposed as a potential therapeutic target in bladder cancer. We characterized the expression of components of the IGF pathway – insulin growth factor receptors (INSR, IGF1R, IGF2R), ligands (INS, IGF1, IGF2), and binding proteins (IGFBP1-7, IGF2BP1-3) – in bladder cancer and its correlation with IGF1R activation, and the anti-proliferative efficacy of an IGF1R kinase inhibitor in this setting.

Biau J., Chautard E., De Koning L., Court F., Pereira B., Verrelle P., Dutreix M. (2017 Jul 1)
Predictive biomarkers of resistance to hypofractionated radiotherapy in high grade glioma
RADIATION ONCOLOGY : 12 : 123 : DOI : 10.1186/s13014-017-0858-0

Summary

Background: Radiotherapy plays a major role in the management of high grade glioma. However, the radioresistance of glioma cells limits its efficiency and drives recurrence inside the irradiated tumor volume leading to poor outcome for patients. Stereotactic hypofractionated radiotherapy is one option for recurrent high grade gliomas. Optimization of hypofractionated radiotherapy with new radiosensitizing agents requires the identification of robust druggable targets involved in radioresistance.

Methods: We generated 11 xenografted glioma models: 6 were derived from cell lines (1 WHO grade III and 5 grade IV) and 5 were patient derived xenografts (2 WHO grade III and 3 grade IV). Xenografts were treated by hypofractionated radiotherapy (6x5Gy). We searched for 89 biomarkers of radioresistance (39 total proteins, 26 phosphoproteins and 24 ratios of phosphoproteins on total proteins) using Reverse Phase Protein Array.

Results: Both type of xenografted models showed equivalent spectrum of sensitivity and profile of response to hypofractionated radiotherapy. We report that Phospho-EGFR/EGFR, Phospho-Chk1/Chk1 and VCP were associated to resistance to hypofractionated radiotherapy.

Conclusions: Several compounds targeting EGFR or CHK1 are already in clinical use and combining them with stereotactic hypofractionated radiotherapy for recurrent high grade gliomas might be of particular interest.

Thierry Launay, Iman Momken, Serge Carreira, Nathalie Mougenot, Xian-Long Zhou, Leanne De Koning, Romain Niel, Bruno Riou, Véronique Billat, Sophie Besse (2017 May 9)
Acceleration-based training: A new mode of training in senescent rats improving performance and left ventricular and muscle functions.
Experimental gerontology : 71-76 : DOI : S0531-5565(17)30017-7

Summary

High intensity training (HIT) has been shown to improve maximal aerobic capacity and muscle protein synthesis but has not yet been investigated in senescent rats. We hypothesized that the change of speed (acceleration) during each bout of HIT acts as a stimulus responsible for the adaptations of the organism to exercise. Twenty two month-old (mo) rats (n=13) were subjected to a short acceleration protocol (20-30min) of exercise, comprising 3 independent bouts of acceleration and compared to an age-matched sedentary group (n=14). The protocol was repeated twice a week for two months. Following the protocol, performance, cardiac function, muscle mechanics, and the cellular and molecular pathways that are implicated in exercise adaptations were investigated. This new training, comprising only 16 sessions, improved maximal oxygen uptake ($\dot{V}O_2$; +6.6%, $p<0.05$), running distance (+95.2%; $p<0.001$), speed (+29.7%; $p<0.01$) and muscle function of 24mo rats in only 8weeks. This new training protocol induced cardiac hypertrophy and improved fractional shortening (47.3% vs. 41.1% in the control group, $p<0.01$) and ejection fraction. Moreover, it also improved the mechanics of skeletal muscle by increasing developed force (+31% vs. the control group, $p<0.05$) and maximal mechanical efficiency, activated the IGF1/mTOR/Akt pathway, and reduced the Smad2/3 pathway. Our results clearly show that the change in speed is a stimulus to control cardiac and skeletal muscle mass. This acceleration-based training is not time-consuming and may be adaptable for athletes, the elderly or chronic disease patients in order to improve strength, oxidative capacity, and quality of life.

Sandra Rebouissou, Tiziana La Bella, Samia Rekik, Sandrine Imbeaud, Anna-Line Calatayud, Nataliya Rohr-Udilova, Yoann Martin, Gabrielle Couchy, Paulette Bioulac-Sage, Bettina Grasl-Kraupp, Leanne de Koning, Nathalie Ganne-Carrié, Jean-Charles Nault, Marianne Ziol, Jessica Zucman-Rossi (2017 Mar 2)
Proliferation Markers Are Associated with MET Expression in Hepatocellular Carcinoma and Predict Tivantinib Sensitivity .
Clinical cancer research : an official journal of the American Association for Cancer Research : 4364-4375 : DOI : 10.1158/1078-0432.CCR-16-3118

Summary

Tivantinib was initially reported as a selective MET inhibitor and is under phase III evaluation in “MET-high” hepatocellular carcinoma (HCC) patients. However, it has been also proposed as an antimitotic agent. We aimed to evaluate the antitumor effect of tivantinib in HCC cells by combining pharmacologic and molecular profiling. Sensitivity to tivantinib, JNJ-38877605,

PHA-665752, vinblastine, and paclitaxel was tested in a panel of 35 liver cancer cell lines analyzed with exome sequencing, mRNA expression of 188 genes, and protein expression. Drug effect was investigated by Western blot analysis and mitotic index quantification. Expression of candidate biomarkers predicting drug response was analyzed in 310 HCCs. Tivantinib sensitivity profiles in the 35 cell lines were similar to those obtained with antimitotic drugs. It induced blockage of cell mitosis, and high cell proliferation was associated with sensitivity to tivantinib, vinblastine, and paclitaxel. In contrast, tivantinib did not suppress MET signaling, and selective MET inhibitors demonstrated an antiproliferative effect only in MHCC97H, the unique cell line displaying gene amplification. HCC tumors with high expression of cell proliferation genes defined a group of patients with poor survival. Interestingly, highly proliferative tumors also demonstrated high MET expression, likely explaining better therapeutic response of MET-high HCC patients to tivantinib. Tivantinib acts as an antimitotic compound, and cell proliferation markers are the best predictors of its antitumor efficacy in cell lines. Ki67 expression should be tested in clinical trials to predict tivantinib response. .

Year of publication 2016

Robin Tranchant, Lisa Quetel, Anne Tallet, Clement Meiller, Annie Renier, Leanne de Koning, Aurelien de Reynies, Francoise Le Pimpec-Barthes, Jessica Zucman-Rossi, Marie-Claude Jaurand, Didier Jean (2016 Dec 23)

Co-occurring Mutations of Tumor Suppressor Genes, and , in Malignant Pleural Mesothelioma.

Clinical cancer research : an official journal of the American Association for Cancer Research : 3191-3202 : DOI : 10.1158/1078-0432.CCR-16-1971

Summary

To better define malignant pleural mesothelioma (MPM) heterogeneity and identify molecular subtypes of MPM, we focus on the tumor suppressor gene , a member of the Hippo signaling pathway, which plays a key role in mesothelial carcinogenesis. Sixty-one MPM primary cultures established in our laboratory were screened for mutations in Gene inactivation was modeled using siRNAs. Gene and protein expressions were analyzed by quantitative RT-PCR, Western blot analysis, and reverse phase protein array. Cell proliferation, viability, apoptosis, mobility, and invasion were determined after siRNA knockdown or YAP (verteporfin), mTOR (rapamycin), and mTOR/PI3K/AKT (PF-04691502) inhibitor treatment. The gene was altered in 11% of MPM by point mutations and large exon deletions. Genetic data coupled with transcriptomic data allowed the identification of a new MPM molecular subgroup, C2, characterized by a co-occurring mutation in the and genes in the same MPM. MPM patients of this subgroup presented a poor prognosis. Coinactivation of and leads to loss of cell contact inhibition between MPM cells. Hippo signaling pathway activity, mTOR expression, and phosphorylation were altered in the C2 MPM subgroup. MPMs of this new subgroup show higher sensitivity to PF-04691502 inhibitor. The gene was identified as a potential biomarker of the C2 MPM subgroup and PF-04691502 sensitivity. We identified a new MPM molecular subgroup that shares common genetic and transcriptomic characteristics. Our results made it possible to highlight a greater sensitivity to an anticancer compound for this MPM

subgroup and to identify a specific potential biomarker. .

Sanne Samuels, Balazs Balint, Heiko von der Leyen, Philippe Hupé, Leanne de Koning, Choumouss Kamoun, Windy Luscap-Rondof, Ulrike Wittkop, Ksenia Bagrintseva, Marina Popovic, Atttila Kereszt, Els Berns, Gemma G Kenter, Ekaterina S Jordanova, Maud Kamal, Susy Scholl (2016 Nov 23)
Precision medicine in cancer: challenges and recommendations from an EU-funded cervical cancer biobanking study.
British journal of cancer : DOI : 10.1038/bjc.2016.340

Summary

Cervical cancer (CC) remains a leading cause of gynaecological cancer-related mortality worldwide. CC pathogenesis is triggered when human papillomavirus (HPV) inserts into the genome, resulting in tumour suppressor gene inactivation and oncogene activation. Collecting tumour and blood samples is critical for identifying these genetic alterations.

Julian Biau, Emmanuel Chautard, Frank Court, Bruno Pereira, Pierre Verrelle, Flavien Devun, Leanne De Koning, Marie Dutreix (2016 Aug 29)
Global Conservation of Protein Status between Cell Lines and Xenografts.
Translational oncology : 313-321 : DOI : S1936-5233(16)30044-4

Summary

Common preclinical models for testing anticancer treatment include cultured human tumor cell lines in monolayer, and xenografts derived from these cell lines in immunodeficient mice. Our goal was to determine how similar the xenografts are compared with their original cell line and to determine whether it is possible to predict the stability of a xenograft model beforehand. We studied a selection of 89 protein markers of interest in 14 human cell cultures and respective subcutaneous xenografts using the reverse-phase protein array technology. We specifically focused on proteins and posttranslational modifications involved in DNA repair, PI3K pathway, apoptosis, tyrosine kinase signaling, stress, cell cycle, MAPK/ERK signaling, SAPK/JNK signaling, NFκB signaling, and adhesion/cytoskeleton. Using hierarchical clustering, most cell culture-xenograft pairs cluster together, suggesting a global conservation of protein signature. Particularly, Akt, NFkB, EGFR, and Vimentin showed very stable protein expression and phosphorylation levels highlighting that 4 of 10 pathways were highly correlated whatever the model. Other proteins were heterogeneously conserved depending on the cell line. Finally, cell line models with low Akt pathway activation and low levels of Vimentin gave rise to more reliable xenograft models. These results may be useful for the extrapolation of cell culture experiments to in vivo models in novel targeted drug discovery.

Guillaume Carita, Estelle Frisch-Dit-Leitz, Ahmed Dahmani, Chloé Raymondie, Nathalie Cassoux, Sophie Piperno-Neumann, Fariba Némati, Cécile Laurent, Leanne De Koning, Ensar Halilovic, Sebastien Jeay, Andrew Wylie, Caroline Emery, Sergio Roman-Roman, Marie Schoumacher, Didier Decaudin (2016 Aug 11)

Dual inhibition of protein kinase C and p53-MDM2 or PKC and mTORC1 are novel efficient therapeutic approaches for uveal melanoma.

Oncotarget : 33542-56 : DOI : 10.18632/oncotarget.9552

Summary

Uveal melanoma (UM) is the most common cancer of the eye in adults. Many UM patients develop metastases for which no curative treatment has been identified. Novel therapeutic approaches are therefore urgently needed. UM is characterized by mutations in the genes GNAQ and GNA11 which activate the PKC pathway, leading to the use of PKC inhibitors as a rational strategy to treat UM tumors. Encouraging clinical activity has been noted in UM patients treated with PKC inhibitors. However, it is likely that curative treatment regimens will require a combination of targeted therapeutic agents. Employing a large panel of UM patient-derived xenograft models (PDXs), several PKC inhibitor-based combinations were tested in vivo using the PKC inhibitor AEB071. The most promising approaches were further investigated in vitro using our unique panel of UM cell lines. When combined with AEB071, the two agents CGM097 (p53-MDM2 inhibitor) and RAD001 (mTORC1 inhibitor) demonstrated greater activity than single agents, with tumor regression observed in several UM PDXs. Follow-up studies in UM cell lines on these two drug associations confirmed their combination activity and ability to induce cell death. While no effective treatment currently exists for metastatic uveal melanoma, we have discovered using our unique panel of preclinical models that combinations between PKC/mTOR inhibitors and PKC/p53-MDM2 inhibitors are two novel and very effective therapeutic approaches for this disease. Together, our study reveals that combining PKC and p53-MDM2 or mTORC1 inhibitors may provide significant clinical benefit for UM patients.

Chloé Prunier, Véronique Josserand, Julien Vollaire, Evelyne Beerling, Christos Petropoulos, Olivier Destaing, Christopher Montemagno, Amandine Hurbin, Renaud Prudent, Leanne de Koning, Reuben Kapur, Pascale A Cohen, Corinne Albiges-Rizo, Jean-Luc Coll, Jacco van Rheenen, Marc N Billaud, Laurence Lafanechere (2016 May 25)

LIM kinase inhibitor Pyr1 reduces the growth and metastatic load of breast cancers.

Cancer research : DOI : canres.1864.2015

Summary

LIM kinases (LIMK) are emerging targets for cancer therapy and they function as network hubs to coordinate actin and microtubule dynamics. When LIMK are inhibited, actin microfilaments are disorganized and microtubules are stabilized. Owing to their stabilizing effect on microtubules, LIMK inhibitors may provide an therapeutic strategy to treat taxane-

resistant cancers. In this study, we investigated the effect of LIMK inhibition on breast tumor development and on paclitaxel resistant tumors, using a novel selective LIMK inhibitor termed Pyr1. Treatment of breast cancer cells, including paclitaxel-resistant cells, blocked their invasion and proliferation in vitro and their growth in vivo in tumor xenograft assays. The tumor invasive properties of Pyr1 were investigated in vivo by intravital microscopy of tumor xenografts. A striking change in cell morphology was observed with a rounded phenotype arising in a subpopulation of cells while other cells remained elongated. Notably, although Pyr1 decreased the motility of elongated cells it increased the motility of rounded cells in the tumor. Pyr1 administration prevented the growth of metastasis but not their spread. Overall, our results provided a preclinical proof of concept concerning how a small molecule inhibitor of LIMK kinases may offer a strategy to treat taxane-resistant breast tumors and metastases.

Didier Meseure, Sophie Vacher, François Lallemand, Kinan Drak Alsibai, Rana Hatem, Walid Chemlali, Andre Nicolas, Leanne De Koning, Eric Pasmant, Celine Callens, Rosette Lidereau, Antonin Morillon, Ivan Bieche (2016 May 13)

Prognostic value of a newly identified MALAT1 alternatively spliced transcript in breast cancer.

British journal of cancer : DOI : 10.1038/bjc.2016.123

Summary

Epigenetic deregulation is considered as a new hallmark of cancer. The long non-coding RNA MALAT1 has been implicated in several cancers; however, its role in breast cancer is still little known.

C Swanton, J-C Soria, A Bardelli, A Biankin, C Caldas, S Chandarlapaty, L de Koning, C Dive, J Feunteun, S-Y Leung, R Marais, E R Mardis, N McGranahan, G Middleton, S A Quezada, J Rodón, N Rosenfeld, C Sotiriou, F André (2016 May 5)

Consensus on precision medicine for metastatic cancers: a report from the MAP conference.

Annals of oncology : official journal of the European Society for Medical Oncology / ESMO : DOI : mdw192

Summary

Recent advances in biotechnologies have led to the development of multiplex genomic and proteomic analyses for clinical use. Nevertheless, guidelines are currently lacking to determine which molecular assays should be implemented in metastatic cancers. The first MAP conference was dedicated to exploring the use of genomics to better select therapies in the treatment of metastatic cancers. Sixteen consensus items were covered. There was a consensus that new technologies like next-generation sequencing of tumors and ddPCR on circulating free DNA have convincing analytical validity. Further work needs to be

undertaken to establish the clinical utility of liquid biopsies and the added clinical value of expanding from individual gene tests into large gene panels. Experts agreed that standardized bioinformatics methods for biological interpretation of genomic data are needed and that precision medicine trials should be stratified based on the level of evidence available for the genomic alterations identified.

Maria E Lomakina, François Lallemand, Sophie Vacher, Nicolas Molinie, Irene Dang, Wulfran Cacheux, Tamara A Chipysheva, Valeria D Ermilova, Leanne de Koning, Thierry Dubois, Ivan Bièche, Antonina Y Alexandrova, Alexis Gautreau (2016 Feb 12)
Arpin downregulation in breast cancer is associated with poor prognosis.
British journal of cancer : 545-53 : DOI : 10.1038/bjc.2016.18

Summary

The Arp2/3 complex is required for cell migration and invasion. The Arp2/3 complex and its activators, such as the WAVE complex, are deregulated in diverse cancers. Here we investigate the expression of Arpin, the Arp2/3 inhibitory protein that antagonises the WAVE complex.

Christophe Couderc, Alizée Boin, Laetitia Fuhrmann, Anne Vincent-Salomon, Vinay Mandati, Yann Kieffer, Fatima Mechta-Grigoriou, Laurence Del Maestro, Philippe Chavrier, David Vallerand, Isabelle Brito, Thierry Dubois, Leanne De Koning, Daniel Bouvard, Daniel Louvard, Alexis Gautreau, Dominique Lallemand (2016 Jan 26)
AMOTL1 integrates Hippo signaling to promote breast cancer progression by inducing tumor cell proliferation and migration
Neoplasia (New York, N.Y.) : 10-24 : DOI : 10.1016/j.neo.2015.11.010

Summary

The Hippo signaling network is a key regulator of cell fate. In the recent years, it was shown that its implication in cancer goes well beyond the sole role of YAP transcriptional activity and its regulation by the canonical MST/LATS kinase cascade. Here we show that the motin family member AMOTL1 is an important effector of Hippo signaling in breast cancer. AMOTL1 connects Hippo signaling to tumor cell aggressiveness. We show that both canonical and noncanonical Hippo signaling modulates AMOTL1 levels. The tumor suppressor Merlin triggers AMOTL1 proteasomal degradation mediated by the NEDD family of ubiquitin ligases through direct interaction. In parallel, YAP stimulates AMOTL1 expression. The loss of Merlin expression and the induction of Yap activity that are frequently observed in breast cancers thus result in elevated AMOTL1 levels. AMOTL1 expression is sufficient to trigger tumor cell migration and stimulates proliferation by activating c-Src. In a large cohort of human breast tumors, we show that AMOTL1 protein levels are upregulated during cancer progression and that, importantly, the expression of AMOTL1 in lymph node metastasis appears predictive of the risk of relapse. Hence we uncover an important mechanism by which Hippo signaling

promotes breast cancer progression by modulating the expression of AMOTL1.