Année de publication : 2021

Elodie Montaudon, Rania El Botty, Sophie Vacher, Olivier Déas, Adnan Naguez, Sophie Chateau-Joubert, Damien Treguer, Ludmilla de Plater, Leïla Zemoura, Fariba Némati, André Nicolas, Alain Chapelier, Alain Livartowski, Stefano Cairo, Catherine Daniel, Marie Brevet, Elisabetta Marangoni, Didier Meseure, Sergio Roman-Roman, Ivan Bieche, Nicolas Girard, Didier Decaudin (2021 Apr 23)

High and synergistic activity between mTORC1 and PLK1 inhibition in adenocarcinoma NSCLC.

Oncotarget : 859-872 : DOI : 10.18632/oncotarget.27930

Résumé

Significant rational is available for specific targeting of PI3K/AKT/mTOR pathway in the treatment of non-small cell lung cancer (NSCLC). However, almost all clinical trials that have evaluated Pi3K pathway-based monotherapies/combinations did not observe an improvement of patient's outcome. The aim of our study was therefore to define combination of treatment based on the determination of predictive markers of resistance to the mTORC1 inhibitor RAD001/Everolimus. An study showed high efficacy of RAD001 in NSCLC Patient-Derived Xenografts (PDXs). When looking at biomarkers of resistance by RT-PCR study, three genes were found to be highly expressed in resistant tumors, i.e., , , and . We have then focused our study on the combination of RAD001 + Volasertib, a PLK1 inhibitor, and observed a high antitumor activity of the combination in comparison to each monotherapy; similarly, a clear synergistic effect between the two compounds was found in an study. Pharmacodynamics study demonstrated that this synergy was due to (1) tumor vascularization decrease, increase of the HIF1 protein expression and decrease of the intracellular pH, and (2) decrease of the Carbonic Anhydrase 9 (CAIX) protein that could not correct intracellular acidosis. In conclusion, all these preclinical data strongly suggest that the inhibition of mTORC1 and PLK1 proteins may be a promising therapeutic approach for NSCLC patients.

Michalina Janiszewska, Shayna Stein, Otto Metzger Filho, Jennifer Eng, Natalie L Kingston, Nicholas W Harper, Inga H Rye, Maša Alečković, Anne Trinh, Katherine C Murphy, Elisabetta Marangoni, Simona Cristea, Benjamin Oakes, Eric P Winer, Ian Krop, Hege G Russnes, Paul T Spellman, Elmar Bucher, Zhi Hu, Koei Chin, Joe W Gray, Franziska Michor, Kornelia Polyak (2021 Apr 22)

The impact of tumor epithelial and microenvironmental heterogeneity on treatment responses in HER2-positive breast cancer.

JCI insight : DOI : 10.1172/jci.insight.147617

Résumé

Despite the availability of multiple HER2-targeted treatments, therapeutic resistance in HER2+ breast cancer remains a clinical challenge. Intratumor heterogeneity for HER2 and

resistance-conferring mutations (e.g., PIK3CA) have been investigated in response and resistance to HER2-targeting agents, while the role of divergent cellular phenotypes and tumor epithelial-stromal cell interactions is less well understood. Here, we assessed the effect of intratumor cellular genetic heterogeneity for ERBB2 copy number and PIK3CA mutation on different types of neoadjuvant HER2-targeting therapies and clinical outcome in HER2+ breast cancer. We found that the frequency of cells lacking HER2 was a better predictor of response to HER2-targeted treatment than intratumor heterogeneity. We also compared the efficacy of different therapies in the same tumor using patient-derived xenograft models of heterogeneous HER2+ breast cancer and single cell approaches. Stromal determinants were better predictors of response than tumor epithelial cells, and we identified alveolar epithelial and fibroblastic reticular cells as well as Lyve1+ macrophages as putative drivers of therapeutic resistance. Our results demonstrate that both pre-existing and acquired resistance to HER2-targeting agents involves multiple mechanisms including the tumor microenvironment. Furthermore, our data also suggest that intratumor heterogeneity for HER2 should be incorporated into treatment design.

Jeremy Bigot, Ana I Lalanne, Francesca Lucibello, Paul Gueguen, Alexandre Houy, Stephane Dayot, Olivier Ganier, Jules Gilet, Jimena Tosello, Fariba Nemati, Gaelle Pierron, Joshua J Waterfall, Raymond Barnhill, Sophie Gardrat, Sophie Piperno-Neumann, Tatiana Popova, Vanessa Masson, Damarys Loew, Pascale Mariani, Nathalie Cassoux, Sebastian Amigorena, Manuel Rodrigues, Samar Alsafadi, Marc-Henri Stern, Olivier Lantz (2021 Apr 3)

Splicing patterns in SF3B1 mutated uveal melanoma generate shared immunogenic tumor-specific neo-epitopes.

Cancer discovery : DOI : candisc.0555.2020

Résumé

Disruption of splicing patterns due to mutations of genes coding splicing factors in tumors represents a potential source of tumor neo-antigens, which would be both public (shared between patients) and tumor-specific (not expressed in normal tissues). In this study, we show that mutations of the splicing factor SF3B1 in uveal melanoma (UM) generate such immunogenic neo-antigens. Memory CD8+ T cells specific for these neo-antigens are preferentially found in 20% of UM patients bearing SF3B1 mutated tumors. Single cell analyses of neo-epitope specific T cells from the blood identified large clonal T cell expansions, with distinct effector transcription patterns. Some of these expanded TCRs are also present in the corresponding tumors. CD8+ T cell clones specific for the neo-epitopes specifically recognize and kill SF3B1-mutated tumor cells, supporting the use of this new family of neo-antigens as therapeutic targets.

Virginie Mieulet, Camille Garnier, Yann Kieffer, Thomas Guilbert, Fariba Nemati, Elisabetta Marangoni, Gilles Renault, Foucauld Chamming's, Anne Vincent-Salomon, Fatima Mechta-Grigoriou (2021 Feb 19)

Stiffness increases with myofibroblast content and collagen density in mesenchymal high grade serous ovarian cancer.
Scientific reports : 4219 : DOI : 10.1038/s41598-021-83685-0

Résumé

Women diagnosed with high-grade serous ovarian cancers (HGSOC) are still likely to exhibit a bad prognosis, particularly when suffering from HGSOC of the Mesenchymal molecular subtype (50% cases). These tumors show a desmoplastic reaction with accumulation of extracellular matrix proteins and high content of cancer-associated fibroblasts. Using patient-derived xenograft mouse models of Mesenchymal and Non-Mesenchymal HGSOC, we show here that HGSOC exhibit distinct stiffness depending on their molecular subtype. Indeed, tumor stiffness strongly correlates with tumor growth in Mesenchymal HGSOC, while Non-Mesenchymal tumors remain soft. Moreover, we observe that tumor stiffening is associated with high stromal content, collagen network remodeling, and MAPK/MEK pathway activation. Furthermore, tumor stiffness accompanies a glycolytic metabolic switch in the epithelial compartment, as expected based on Warburg's effect, but also in stromal cells. This effect is restricted to the central part of stiff Mesenchymal tumors. Indeed, stiff Mesenchymal tumors remain softer at the periphery than at the core, with stromal cells secreting high levels of collagens and showing an OXPHOS metabolism. Thus, our study suggests that tumor stiffness could be at the crossroad of three major processes, i.e. matrix remodeling, MEK activation and stromal metabolic switch that might explain at least in part Mesenchymal HGSOC aggressiveness.

Hazel M Quinn, Regina Vogel, Oliver Popp, Philipp Mertins, Linxiang Lan, Clemens Messerschmidt, Alexandro Landshammer, Kamil Lisek, Sophie Chateau-Joubert, Elisabetta Marangoni, Elle Koren, Yaron Fuchs, Walter Birchmeier (2021 Feb 12)
YAP and β-catenin cooperate to drive oncogenesis in basal breast cancer.
Cancer research : DOI : canres.2801.2020

Résumé

Targeting cancer stem cells (CSC) can serve as an effective approach toward limiting resistance to therapies. While basal-like (triple-negative) breast cancers encompass cells with CSC features, rational therapies remain poorly established. We show here that the receptor tyrosine kinase Met promotes YAP activity in basal-like breast cancer and find enhanced YAP activity within the CSC population. Interfering with YAP activity delayed basal-like cancer formation, prevented luminal to basal trans-differentiation, and reduced CSC. YAP knockout mammary glands revealed a decrease in β-catenin target genes, suggesting that YAP is required for nuclear β-catenin activity. Mechanistically, nuclear YAP interacted with β-catenin and TEAD4 at gene regulatory elements. Proteomic patient data revealed an upregulation of the YAP signature in basal-like breast cancers. Our findings demonstrate that in basal-like breast cancers, β-catenin activity is dependent on YAP signalling and controls the CSC program. These findings suggest that targeting the YAP/TEAD4/β-catenin complex offers a potential therapeutic strategy for eradicating CSCs in basal-like breast cancers.

Stijn Moens, Peihua Zhao, Maria Francesca Baietti, Oliviero Marinelli, Delphi Van Haver, Francis Impens, Giuseppe Floris, Elisabetta Marangoni, Patrick Neven, Daniela Annibali, Anna A Sablina, Frédéric Amant (2021 Feb 5)

The mitotic checkpoint is a targetable vulnerability of carboplatin-resistant triple negative breast cancers.

Scientific reports : 3176 : DOI : 10.1038/s41598-021-82780-6

Résumé

Triple-negative breast cancer (TNBC) is the most aggressive breast cancer subtype, lacking effective therapy. Many TNBCs show remarkable response to carboplatin-based chemotherapy, but often develop resistance over time. With increasing use of carboplatin in the clinic, there is a pressing need to identify vulnerabilities of carboplatin-resistant tumors. In this study, we generated carboplatin-resistant TNBC MDA-MB-468 cell line and patient derived TNBC xenograft models. Mass spectrometry-based proteome profiling demonstrated that carboplatin resistance in TNBC is linked to drastic metabolism rewiring and upregulation of anti-oxidative response that supports cell replication by maintaining low levels of DNA damage in the presence of carboplatin. Carboplatin-resistant cells also exhibited dysregulation of the mitotic checkpoint. A kinome shRNA screen revealed that carboplatin-resistant cells are vulnerable to the depletion of the mitotic checkpoint regulators, whereas the checkpoint kinases CHEK1 and WEE1 are indispensable for the survival of carboplatin-resistant cells in the presence of carboplatin. We confirmed that pharmacological inhibition of CHEK1 by prexasertib in the presence of carboplatin is well tolerated by mice and suppresses the growth of carboplatin-resistant TNBC xenografts. Thus, abrogation of the mitotic checkpoint by CHEK1 inhibition re-sensitizes carboplatin-resistant TNBCs to carboplatin and represents a potential strategy for the treatment of carboplatin-resistant TNBCs.

Weijing Han, Rania El Botty, Elodie Montaudon, Laurent Malaquin, Frederic Deschaseaux, Nicolas Espagnolle, Elisabetta Marangoni, Paul Cottu, Gérard Zalcman, Maria Carla Parrini, Franck Assayag, Luc Sensebe, Pascal Silberzan, Anne Vincent-Salomon, Guillaume Dutertre, Sergio Roman-Roman, Stephanie Descroix, Jacques Camonis (2021 Jan 9)

In vitro bone metastasis dwelling in a 3D bioengineered niche.

Biomaterials : 120624 : DOI : S0142-9612(20)30871-1

Résumé

Bone is the most frequent metastasis site for breast cancer. As well as dramatically increasing disease burden, bone metastases are also an indicator of poor prognosis. One of the main challenges in investigating bone metastasis in breast cancer is engineering in vitro models that replicate the features of in vivo bone environments. Such in vitro models ideally enable the biology of the metastatic cells to mimic their in vivo behavior as closely as possible. Here, taking benefit of cutting-edge technologies both in microfabrication and cancer cell biology, we have developed an in vitro breast cancer bone-metastasis model. To

do so we first 3D printed a bone scaffold that reproduces the trabecular architecture and that can be conditioned with osteoblast-like cells, a collagen matrix, and mineralized calcium. We thus demonstrated that this device offers an adequate soil to seed primary breast cancer bone metastatic cells. In particular, patient-derived xenografts being considered as a better approach than cell lines to achieve clinically relevant results, we demonstrate the ability of this biomimetic bone niche model to host patient-derived xenografted metastatic breast cancer cells. These patient-derived xenograft cells show a long-term survival in the bone model and maintain their cycling propensity, and exhibit the same modulated drug response as in vivo. This experimental system enables access to the idiosyncratic features of the bone microenvironment and cancer bone metastasis, which has implications for drug testing.

Xing Yi Woo, Jessica Giordano, Anuj Srivastava, Zi-Ming Zhao, Michael W Lloyd, Roebi de Bruijn, Yun-Suhk Suh, Rajesh Patidar, Li Chen, Sandra Scherer, Matthew H Bailey, Chieh-Hsiang Yang, Emilio Cortes-Sanchez, Yuanxin Xi, Jing Wang, Jayamanna Wickramasinghe, Andrew V Kossenkov, Vito W Rebecca, Hua Sun, R Jay Mashl, Sherri R Davies, Ryan Jeon, Christian Frech, Jelena Randjelovic, Jacqueline Rosains, Francesco Galimi, Andrea Bertotti, Adam Lafferty, Alice C O'Farrell, Elodie Modave, Diether Lambrechts, Petra Ter Brugge, Violeta Serra, Elisabetta Marangoni, Rania El Botty, Hyunsoo Kim, Jong-Il Kim, Han-Kwang Yang, Charles Lee, Dennis A Dean, Brandi Davis-Dusenbery, Yvonne A Evrard, James H Doroshow, Alana L Welm, Bryan E Welm, Michael T Lewis, Bingliang Fang, Jack A Roth, Funda Meric-Bernstam, Meenhard Herlyn, Michael A Davies, Li Ding, Shunqiang Li, Ramaswamy Govindan, Claudio Isella, Jeffrey A Moscow, Livio Trusolino, Annette T Byrne, Jos Jonkers, Carol J Bult, Enzo Medico, Jeffrey H Chuang, , (2021 Jan 8)

Conservation of copy number profiles during engraftment and passaging of patient-derived cancer xenografts.

Nature genetics : 86-99 : DOI : 10.1038/s41588-020-00750-6

Résumé

Patient-derived xenografts (PDXs) are resected human tumors engrafted into mice for preclinical studies and therapeutic testing. It has been proposed that the mouse host affects tumor evolution during PDX engraftment and propagation, affecting the accuracy of PDX modeling of human cancer. Here, we exhaustively analyze copy number alterations (CNAs) in 1,451 PDX and matched patient tumor (PT) samples from 509 PDX models. CNA inferences based on DNA sequencing and microarray data displayed substantially higher resolution and dynamic range than gene expression-based inferences, and they also showed strong CNA conservation from PTs through late-passage PDXs. CNA recurrence analysis of 130 colorectal and breast PT/PDX-early/PDX-late trios confirmed high-resolution CNA retention. We observed no significant enrichment of cancer-related genes in PDX-specific CNAs across models. Moreover, CNA differences between patient and PDX tumors were comparable to variations in multiregion samples within patients. Our study demonstrates the lack of systematic copy number evolution driven by the PDX mouse host.

Alberto Fogagnolo, Salvatore Grasso, Martin Dres, Loreto Gesualdo, Francesco Murgolo, Elena Morelli, Irene Ottaviani, Elisabetta Marangoni, Carlo Alberto Volta, Savino Spadaro (2021 Jan 1)
Focus on renal blood flow in mechanically ventilated patients with SARS-CoV-2: a prospective pilot study.
Journal of clinical monitoring and computing : DOI : 10.1007/s10877-020-00633-5

Résumé

Mechanically ventilated patients with ARDS due to the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) seem particularly susceptible to AKI. Our hypothesis was that the renal blood flow could be more compromised in SARS-CoV-2 patients than in patients with « classical » ARDS. We compared the renal resistivity index (RRI) and the renal venous flow (RVF) in ARDS patients with SARS-CoV-2 and in ARDS patients due to other etiologies. Prospective, observational pilot study performed on 30 mechanically ventilated patients (15 with SARS-COV-2 ARDS and 15 with ARDS). Mechanical ventilation settings included constant-flow controlled ventilation, a tidal volume of 6 ml/kg of ideal body weight and the PEEP level titrated to the lowest driving pressure. Ultrasound Doppler measurements of RRI and RVF pattern were performed in each patient. Patients with SARS-COV-2 ARDS had higher RRI than patients with ARDS (0.71[0.67-0.78] vs 0.64[0.60-0.74], p = 0.04). RVF was not-continuous in 9/15 patients (71%) in the SARS-COV-2 ARDS group and in and 5/15 (33%) in the ARDS group (p = 0.27). A linear correlation was found between PEEP and RRI in patients with SARS-COV-2 ARDS (r = 0.31; p = 0.03) but not in patients with ARDS. Occurrence of AKI was 53% in patients with SARS-COV-2 ARDS and 33% in patients with ARDS (p = 0.46). We found a more pronounced impairment in renal blood flow in mechanically ventilated patients with SARS-COV-2 ARDS, compared with patients with « classical » ARDS.

Année de publication : 2020

Rémi Letestu, Abdelmalek Dahmani, Marouane Boubaya, Lucile Baseggio, Lydia Campos, Bernard Chatelain, Agathe Debliquis, Bernard Drénou, Marie-Christine Jacob, Eric Legac, Magali Le Garff-Tavernier, Anne-Catherine Lhoumeau, Claire Quiney, Nelly Robillard, Michel Ticchioni, Carmen Aanei, Sandrine Katsahian, Roselyne Delepine, Sandrine Vaudaux, Valérie Rouillé, Marie-Christine Béné, Caroline Dartigeas, Eric Van Den Neste, Stéphane Leprêtre, Pierre Feugier, Guillaume Cartron, Véronique Leblond, Vincent Lévy, Florence Cymbalista, (2020 Sep 16)
Prognostic value of high-sensitivity measurable residual disease assessment after front-line chemoimmunotherapy in chronic lymphocytic leukemia.
Leukemia : DOI : 10.1038/s41375-020-01009-z

Résumé

Measurable residual disease (MRD) status is widely adopted in clinical trials in patients with chronic lymphocytic leukemia (CLL). Findings from FILO group trials (CLL2007FMP, CLL2007SA, CLL2010FMP) enabled investigation of the prognostic value of high-sensitivity (0.7×10) MRD assessment using flow cytometry, in blood (N = 401) and bone marrow

(N = 339), after fludarabine, cyclophosphamide, and rituximab (FCR)-based chemoimmunotherapy in a homogeneous population with long follow-up (median 49.5 months). Addition of low-level positive MRD < 0.01% to MRD ≥ 0.01% increased the proportion of cases with positive MRD in blood by 39% and in bone marrow by 27%. Compared to low-level positive MRD < 0.01%, undetectable MRD was associated with significantly longer progression-free survival (PFS) when using blood (72.2 versus 42.7 months; hazard ratio 0.40, p = 0.0003), but not when using bone marrow. Upon further stratification, positive blood MRD at any level, compared to undetectable blood MRD, was associated with shorter PFS irrespective of clinical complete or partial remission, and a lower 5-year PFS rate irrespective of IGHV-mutated or -unmutated status (all p < 0.05). In conclusion, high-sensitivity (0.0007%) MRD assessment in blood yielded additional prognostic information beyond the current standard sensitivity (0.01%). Our approach provides a model for future determination of the optimal MRD investigative strategy for any regimen.

Elodie Montaudon, Joanna Nikitorowicz-Buniak, Laura Sourd, Ludivine Morisset, Rania El Botty, Léa Huguet, Ahmed Dahmani, Pierre Painsec, Fariba Nemati, Sophie Vacher, Walid Chemlali, Julien Masliah-Planchon, Sophie Château-Joubert, Camilla Rega, Mariana Ferreira Leal, Nikiana Simigdala, Sunil Pancholi, Ricardo Ribas, André Nicolas, Didier Meseure, Anne Vincent-Salomon, Cécile Reyes, Audrey Rapinat, David Gentien, Thibaut Larcher, Mylène Bohec, Sylvain Baulande, Virginie Bernard, Didier Decaudin, Florence Coussy, Muriel Le Romancer, Guillaume Dutertre, Zakia Tariq, Paul Cottu, Keltouma Driouch, Ivan Bièche, Lesley-Ann Martin, Elisabetta Marangoni (2020 Aug 15)

PLK1 inhibition exhibits strong anti-tumoral activity in CCND1-driven breast cancer metastases with acquired palbociclib resistance.

Nature communications : 4053 : DOI : 10.1038/s41467-020-17697-1

Résumé

A significant proportion of patients with oestrogen receptor (ER) positive breast cancers (BC) develop resistance to endocrine treatments (ET) and relapse with metastatic disease. Here we perform whole exome sequencing and gene expression analysis of matched primary breast tumours and bone metastasis-derived patient-derived xenografts (PDX). Transcriptomic analyses reveal enrichment of the G2/M checkpoint and up-regulation of Polo-like kinase 1 (PLK1) in PDX. PLK1 inhibition results in tumour shrinkage in highly proliferating CCND1-driven PDX, including different RB-positive PDX with acquired palbociclib resistance. Mechanistic studies in endocrine resistant cell lines, suggest an ER-independent function of PLK1 in regulating cell proliferation. Finally, in two independent clinical cohorts of ER positive BC, we find a strong association between high expression of PLK1 and a shorter metastases-free survival and poor response to anastrozole. In conclusion, our findings support clinical development of PLK1 inhibitors in patients with advanced CCND1-driven BC, including patients progressing on palbociclib treatment.

Jerome Paillassa, Edouard Cornet, Stephanie Noel, Cecile Tomowiak, Stephane Lepretre, Sandrine Vaudaux, Jehan Dupuis, Alain Devidas, Bertrand Joly, Charlotte Petitdidier-Lionnet, Stephanie Haiat, Clara Mariette, Catherine Thieblemont, Didier Decaudin, Patricia Validire-Charpy, Bernard Drenou, Jean-Claude Eisenmann, Mario Ojeda Uribe, Agnès Olivrie, Mohamed Touati, Olivier Lambotte, Olivier Hermine, Jean-Michel Karsenti, Pierre Feugier, Willy Vaillant, Jean Gutnecht, Eric Lippert, Fabienne Huysman, Kamel Ghomari, Marouane Boubaya, Vincent Levy, Jeremie Riou, Gandhi Damaj, Aline Tanguy-Schmidt, Mathilde Hunault-Berger, Xavier Troussard (2020 May 29)

Analysis of a cohort of 279 patients with hairy-cell leukemia (HCL): 10 years of follow-up.

Blood cancer journal : 62 : DOI : 10.1038/s41408-020-0328-z

Résumé

In total, 279 patients with hairy-cell leukemia (HCL) were analyzed, with a median follow-up of 10 years. Data were collected up to June 2018. We analyzed responses to treatment, relapses, survival, and the occurrence of second malignancies during follow-up. The median age was 59 years. In total, 208 patients (75%) were treated with purine analogs (PNAs), either cladribine (159) or pentosatin (49), as the first-line therapy. After a median follow-up of 127 months, the median overall survival was 27 years, and the median relapse-free survival (RFS) was 11 years. The cumulative 10-year relapse incidence was 39%. In patients receiving second-line therapy, the median RFS was 7 years. For the second-line therapy, using the same or another PNA was equivalent. We identified 68 second malignancies in 59 patients: 49 solid cancers and 19 hematological malignancies. The 10-year cumulative incidences of cancers, solid tumors, and hematological malignancies were 15%, 11%, and 5.0%, respectively, and the standardized incidence ratios were 2.22, 1.81, and 6.67, respectively. In multivariate analysis, PNA was not a risk factor for second malignancies. HCL patients have a good long-term prognosis. PNAs are the first-line treatment. HCL patients require long-term follow-up because of their relatively increased risk of second malignancies.

Mingjun Bi, Zhao Zhang, Yi-Zhou Jiang, Pengya Xue, Hu Wang, Zhao Lai, Xiaoyong Fu, Carmine De Angelis, Yue Gong, Zhen Gao, Jianhua Ruan, Victor X Jin, Elisabetta Marangoni, Elodie Montaudon, Christopher K Glass, Wei Li, Tim Hui-Ming Huang, Zhi-Ming Shao, Rachel Schiff, Lizhen Chen, Zhijie Liu (2020 May 20)

Enhancer reprogramming driven by high-order assemblies of transcription factors promotes phenotypic plasticity and breast cancer endocrine resistance.

Nature cell biology : 701-715 : DOI : 10.1038/s41556-020-0514-z

Résumé

Acquired therapy resistance is a major problem for anticancer treatment, yet the underlying molecular mechanisms remain unclear. Using an established breast cancer cellular model, we show that endocrine resistance is associated with enhanced phenotypic plasticity,

indicated by a general downregulation of luminal/epithelial differentiation markers and upregulation of basal/mesenchymal invasive markers. Consistently, similar gene expression changes are found in clinical breast tumours and patient-derived xenograft samples that are resistant to endocrine therapies. Mechanistically, the differential interactions between oestrogen receptor α and other oncogenic transcription factors, exemplified by GATA3 and AP1, drive global enhancer gain/loss reprogramming, profoundly altering breast cancer transcriptional programs. Our functional studies in multiple culture and xenograft models reveal a coordinated role of GATA3 and AP1 in re-organizing enhancer landscapes and regulating cancer phenotypes. Collectively, our study suggests that differential high-order assemblies of transcription factors on enhancers trigger genome-wide enhancer reprogramming, resulting in transcriptional transitions that promote tumour phenotypic plasticity and therapy resistance.

Sunil Pancholi, Ricardo Ribas, Nikiana Simigdala, Eugene Schuster, Joanna Nikitorowicz-Buniak, Anna Ressa, Qiong Gao, Mariana Ferreira Leal, Amandeep Bhamra, Allan Thornhill, Ludivine Morisset, Elodie Montaudon, Laura Sourd, Martin Fitzpatrick, Maarten Altelaar, Stephen R Johnston, Elisabetta Marangoni, Mitch Dowsett, Lesley-Ann Martin (2020 Apr 21)
Tumour kinome re-wiring governs resistance to palbociclib in oestrogen receptor positive breast cancers, highlighting new therapeutic modalities.
Oncogene : 4781-4797 : DOI : 10.1038/s41388-020-1284-6

Résumé

Combination of CDK4/6 inhibitors and endocrine therapy improves clinical outcome in advanced oestrogen receptor (ER)-positive breast cancer, however relapse is inevitable. Here, we show in model systems that other than loss of RB1 few gene-copy number (CN) alterations are associated with irreversible-resistance to endocrine therapy and subsequent secondary resistance to palbociclib. Resistance to palbociclib occurred as a result of tumour cell re-wiring leading to increased expression of EGFR, MAPK, CDK4, CDK2, CDK7, CCNE1 and CCNE2. Resistance altered the ER genome wide-binding pattern, leading to decreased expression of 'classical' oestrogen-regulated genes and was accompanied by reduced sensitivity to fulvestrant and tamoxifen. Persistent CDK4 blockade decreased phosphorylation of tuberous sclerosis complex 2 (TSC2) enhancing EGFR signalling, leading to the re-wiring of ER. Kinome-knockdown confirmed dependency on ERBB-signalling and G2/M-checkpoint proteins such as WEE1, together with the cell cycle master regulator, CDK7. Noteworthy, sensitivity to CDK7 inhibition was associated with loss of ER and RB1 CN. Overall, we show that resistance to CDK4/6 inhibitors is dependent on kinase re-wiring and the redeployment of signalling cascades previously associated with endocrine resistance and highlights new therapeutic networks that can be exploited upon relapse after CDK4/6 inhibition.

F Coussy, R El Botty, M Lavigne, C Gu, L Fuhrmann, A Briaux, L de Koning, A Dahmani, E Montaudon, L Morisset, L Huguet, L Sourd, P Painsec, S Chateau-Joubert, T Larcher, S Vacher, S

Melaabi, A Vincent Salomon, E Marangoni, I Bieche (2020 Feb 24)

Combination of PI3K and MEK inhibitors yields durable remission in PDX models of PIK3CA-mutated metaplastic breast cancers.

Journal of hematology & oncology : 13 : DOI : 10.1186/s13045-020-0846-y

Résumé

Metaplastic breast cancer (MBC) is a rare form of breast cancer characterized by an aggressive clinical presentation, with a poor response to standard chemotherapy. MBCs are typically triple-negative breast cancers (TNBCs), frequently with alterations to genes of the PI3K-AKT-mTOR and RTK-MAPK signaling pathways. The objective of this study was to determine the response to PI3K and MAPK pathway inhibitors in patient-derived xenografts (PDXs) of MBCs with targetable alterations.