Year of publication 2019

F Coussy, L de Koning, M Lavigne, V Bernard, B Ouine, A Boulai, R El Botty, A Dahmani, E Montaudon, F Assayag, L Morisset, L Huguet, L Sourd, P Painsec, C Callens, S Chateau-Joubert, J-L Servely, T Larcher, C Reyes, E Girard, G Pierron, C Laurent, S Vacher, S Baulande, S Melaabi, A Vincent Salomon, D Gentien, V Dieras, I Bieche, E Marangoni (2019 Mar 13)

A large collection of integrated genomically characterized patient-derived xenografts highlighting the heterogeneity of triple-negative breast cancer.

International journal of cancer : DOI : 10.1002/ijc.32266

Summary

Triple-negative breast cancer (TNBC) represents 10% of all breast cancers and is a very heterogeneous disease. Globally, women with TNBC have a poor prognosis, and the development of effective targeted therapies remains a real challenge. Patient-Derived Xenografts (PDX) are clinically relevant models that have emerged as important tools for the analysis of drug activity and predictive biomarker discovery. The purpose of this work was to analyze the molecular heterogeneity of a large panel of TNBC PDX (n=61) in order to test targeted therapies and identify biomarkers of response. At the gene expression level, TNBC PDX represent all of the various TNBC subtypes identified by the Lehmann classification except for immunomodulatory subtype, which is underrepresented in PDX. NGS and copy number data showed a similar diversity of SMGs (Significantly Mutated Gene) and SCNAs (Somatic Copy Number Alteration) in PDX and TCGA TNBC patients. The genes most commonly altered were TP53 and oncogenes and tumor suppressors of the PI3K/AKT/mTOR and MAPK pathways. PDX showed similar morphology and immunohistochemistry markers to those of the original tumors. Efficacy experiments with PI3K and MAPK inhibitor monotherapy or combination therapy showed an antitumor activity in PDX carrying genomic mutations of PIK3CA and NRAS genes.TNBC PDX reproduce the molecular heterogeneity of TNBC patients. This large collection of PDX is a clinically relevant platform for drug testing, biomarker discovery and translational research. KEYS WORD: Triple-negative breast cancer, targeted therapies, patient-derived xenograft (PDX), integrated genomic analysis. This article is protected by copyright. All rights reserved.

Year of publication 2018

Philippe De La Rochere, Silvia Guil-Luna, Didier Decaudin, Georges Azar, Sukhvinder S Sidhu, Eliane Piaggio (2018 Aug 6)

Humanized Mice for the Study of Immuno-Oncology.

Trends in immunology : 748-763 : DOI : S1471-4906(18)30125-X

Summary

Immunotherapy is revolutionizing cancer treatment; however, complete responses are achieved in only a small fraction of patients and tumor types. Thus, there is an urgent need for predictive preclinical models to drive rational immunotherapeutic drug development,

treatment combinations, and to minimize failures in clinical trials. Humanized mouse models (HIS) have been developed to study and modulate the interactions between immune components and tumors of human origin. In this review, we discuss recent advances in the 'humanization' of mouse models to improve the quality of human immune cell reconstitution. We also highlight new insights into the basic mechanisms, and provide a preclinical evaluation of onco-immunotherapies, as well as the limitations thereof, which constitute drivers for the improvement of the models to increase their translational power.

Rania El Botty, Florence Coussy, Rana Hatem, Franck Assayag, Sophie Chateau-Joubert, Jean-Luc Servely, Sophie Leboucher, Charles Fouillade, Sophie Vacher, Bérengère Ouine, Aurélie Cartier, Leanne de Koning, Paul Cottu, Ivan Bièche, Elisabetta Marangoni (2018 Jul 25)

Inhibition of mTOR downregulates expression of DNA repair proteins and is highly efficient against BRCA2-mutated breast cancer in combination to PARP inhibition.

Oncotarget : 29587-29600 : DOI : 10.18632/oncotarget.25640

Summary

Breast cancer is a complex disease in which each patient could present several genetic alterations that are therapeutically relevant in cancers. Here we explored the therapeutic benefit of combining PARP and mTOR inhibitors in a context of DNA repair deficiency and PI3K pathway activation. The combination of everolimus and olaparib was tested in BRCA2-mutated patient-derived xenografts (PDX) carrying alterations in the PI3K/AKT/mTOR pathway. An RPPA analysis of different signalling pathways was performed in untreated and treated xenografts. Everolimus and olaparib showed marked anti-tumor activities in the monotherapy setting and high efficacy when given in combination with 100% of mice showing tumor regressions. The fraction of P-H2AX positive cells was increased in both monotherapy arms and strongly increased in the combination setting. Everolimus given as monotherapy resulted in downregulation of different proteins involved in DNA damage repair, including FANCD2, RAD50 and SUV39H1. In the combination setting, expression of these proteins was almost completely abolished, suggesting convergence of PARP and mTOR in downregulation of DNA damage repair components. In conclusion, our results suggest that combining mTOR and DNA repair inhibition could be a successful strategy to treat a subset of breast cancer with BRCA2 mutation and alterations in the PI3K/AKT/mTOR pathway.

Caroline Spasojevic, Elisabetta Marangoni, Sophie Vacher, Franck Assayag, Didier Meseure, Sophie Château-Joubert, Martine Humbert, Manale Karam, Jean Marc Ricort, Christian Auclair, Marie Regairaz, Ivan Bièche (2018 May 26)

PKD1 is a potential biomarker and therapeutic target in triple-negative breast cancer.

Oncotarget : 23208-23219 : DOI : 10.18632/oncotarget.25292

Summary

Protein Kinase D1 (PKD1) is a serine/threonine kinase encoded by the gene. PKD1 has been previously shown to be a prognostic factor in ERα+ tamoxifen-resistant breast tumors and PKD1 overexpression confers estrogen independence to ERα+ MCF7 cells. In the present study, our goal was to determine whether PKD1 is a prognostic factor and/or a relevant therapeutic target in breast cancer. We analyzed mRNA levels in 527 primary breast tumors. We found that high mRNA levels were significantly and independently associated with a low metastasis-free survival in the whole breast cancer population and in the triple-negative breast cancer (TNBC) subtype specifically. High mRNA levels were also associated with a low overall survival in TNBC. We identified novel PKD1 inhibitors and assessed their antitumor activity in TNBC cell lines and in a TNBC patient-derived xenograft (PDX) model. Pharmacological inhibition and siRNA-mediated depletion of PKD1 reduced colony formation in MDA-MB-436 TNBC cells. PKD1 inhibition also reduced tumor growth in a TNBC PDX model. Together, these results establish PKD1 as a poor prognostic factor and a potential therapeutic target in TNBC.

Didier Decaudin, Rania El Botty, Béré Diallo, Gerald Massonnet, Justine Fleury, Adnan Naguez, Chloé Raymondie, Emma Davies, Aaron Smith, Joanne Wilson, Colin Howes, Paul D Smith, Nathalie Cassoux, Sophie Piperno-Neumann, Sergio Roman-Roman, Fariba Némati (2018 May 19)
Selumetinib-based therapy in uveal melanoma patient-derived xenografts.
Oncotarget : 21674-21686 : DOI : 10.18632/oncotarget.24670

Summary

The prognosis of metastatic uveal melanoma (UM) is among the worst of all human cancers. The identification of near-ubiquitous GNAQ/GNA11 mutations and the activation of MAPK signaling in UM have raised hopes of more effective, targeted therapies, based on MEK inhibition, for example. We evaluated the potential of drug combinations to increase the efficacy of the MEK inhibitor selumetinib (AZD6244, ARRY-142886), in UM cell lines and Patient-Derived Xenografts. We first evaluated the combination of selumetinib and DTIC. We found that DTIC did not improve the or antitumor efficacy of selumetinib, consistent with the outcome of the SUMIT clinical trial assessing the efficacy of this combination in UM. We then tested additional selumetinib combinations with the chemotherapy agent docetaxel, the ERK inhibitor AZ6197, and the mTORC1/2 inhibitor, vistusertib (AZD2014). Combinations of selumetinib with ERK and mTORC1/2 inhibitors appeared to be the most effective in UM PDX models.

Elisabetta Marangoni, Cécile Laurent, Florence Coussy, Rania El-Botty, Sophie Château-Joubert, Jean-Luc Servely, Ludmilla de Plater, Franck Assayag, Ahmed Dahmani, Elodie Montaudon, Fariba Nemati, Justine Fleury, Sophie Vacher, David Gentien, Audrey Rapinat, Pierre Foidart, Nor Eddine Sounni, Agnès Noel, Anne Vincent-Salomon, Marick Lae, Didier Decaudin, Sergio Roman-Roman, Ivan Bièche, Martine Piccart, Fabien Reyal (2018 Feb 22)

Capecitabine Efficacy Is Correlated with TYMP and RB1 Expression in PDX Established from Triple-Negative Breast Cancers.

Clinical cancer research : an official journal of the American Association for Cancer Research : 2605-2615 : DOI : 10.1158/1078-0432.CCR-17-3490

Summary

Triple-negative breast cancer (TNBC) patients with residual disease after neoadjuvant chemotherapy have a poor outcome. We developed patient-derived xenografts (PDX) from residual tumors to identify efficient chemotherapies and predictive biomarkers in a context of resistance to anthracyclines- and taxanes-based treatments. PDX were established from residual tumors of primary breast cancer patients treated in neoadjuvant setting. TNBC PDX were treated by anthracyclines, taxanes, platins, and capecitabine. Predictive biomarkers were identified by transcriptomic and immunohistologic analysis. Downregulation of was performed by siRNA in a cell line established from a PDX. Residual TNBC PDX were characterized by a high tumor take, a short latency, and a poor prognosis of the corresponding patients. With the exception of BRCA1/2-mutated models, residual PDX were resistant to anthracyclines, taxanes, and platins. Capecitabine, the oral prodrug of 5-FU, was highly efficient in 60% of PDX, with two models showing complete responses. Prior treatment of a responder PDX with 5-FU increased expression of thymidylate synthase and decreased efficacy of capecitabine. Transcriptomic and IHC analyses of 32 TNBC PDX, including both residual tumors and treatment-naïve derived tumors, identified RB1 and TYMP proteins as predictive biomarkers for capecitabine response. Finally, knockdown in a cell line established from a capecitabine-responder PDX decreased sensitivity to 5-FU treatment. We identified capecitabine as efficient chemotherapy in TNBC PDX models established from residual disease and resistant to anthracyclines, taxanes, and platins. RB1 positivity and high expression of TYMP were significantly associated with capecitabine response. .

Year of publication 2017

Houcine Bougherara, Fariba Némati, André Nicolas, Gérald Massonnet, Martine Pugnière, Charlotte Ngô, Marie-Aude Le Frère-Belda, Alexandra Leary, Jérôme Alexandre, Didier Meseure, Jean-Marc Barret, Isabelle Navarro-Teulon, André Pèlegrin, Sergio Roman-Roman, Jean-François Prost, Emmanuel Donnadieu, Didier Decaudin (2017 Dec 17)

The humanized anti-human AMHRII mAb 3C23K exerts an anti-tumor activity against human ovarian cancer through tumor-associated macrophages.

Oncotarget : 99950-99965 : DOI : 10.18632/oncotarget.21556

Summary

Müllerian inhibiting substance, also called anti-Müllerian hormone (AMH), inhibits proliferation and induces apoptosis of AMH type II receptor-positive tumor cells, such as human ovarian cancers (OCs). On this basis, a humanized glyco-engineered monoclonal antibody (3C23K) has been developed. The aim of this study was therefore to experimentally confirm the therapeutic potential of 3C23K in human OCs. We first determined by

immunofluorescence, immunohistochemistry and cytofluorometry analyses the expression of AMHRII in patient's tumors and found that a majority (60 to 80% depending on the detection technique) of OCs were positive for this marker. We then provided evidence that the tumor stroma of OC is enriched in tumor-associated macrophages and that these cells are responsible for 3C23K-induced killing of tumor cells through ADCP and ADCC mechanisms. In addition, we showed that 3C23K reduced macrophages induced-T cells immunosuppression. Finally, we evaluated the therapeutic efficacy of 3C23K alone and in combination with a carboplatin-paclitaxel chemotherapy in a panel of OC Patient-Derived Xenografts. In those experiments, we showed that 3C23K significantly increased the proportion and the quality of chemotherapy-based responses. Altogether, our data support the potential interest of AMHRII targeting in human ovarian cancers and the evaluation of 3C23K in further clinical trials.

F Coussy, F Lallemand, S Vacher, A Schnitzler, W Chemlali, M Caly, A Nicolas, S Richon, D Meseure, R El Botty, L De-Plater, L Fuhrmann, T Dubois, S Roman-Roman, V Dangles-Marie, E Marangoni, I Bièche (2017 May 5)
Clinical value of R-spondins in triple-negative and metaplastic breast cancers.
British journal of cancer : 1595-1603 : DOI : 10.1038/bjc.2017.131

Summary

RSPO ligands, activators of the Wnt/β-catenin pathway, are overexpressed in different cancers. The objective of this study was to investigate the role of RSPOs in breast cancer (BC).

Year of publication 2016

Didier Decaudin, Christophe Le Tourneau (2016 Oct 27)
Combinations of targeted therapies in human cancers.
Aging : 2258-2259 : DOI : 10.18632/aging.101085

Summary

T Huibertus van Essen, Sake I van Pelt, Inge H G Bronkhorst, Mieke Versluis, Fariba Némati, Cécile Laurent, Gregorius P M Luyten, Thorbald van Hall, Peter J van den Elsen, Pieter A van der Velden, Didier Decaudin, Martine J Jager (2016 Oct 21)
Upregulation of HLA Expression in Primary Uveal Melanoma by Infiltrating Leukocytes.
PloS one : e0164292 : DOI : 10.1371/journal.pone.0164292

Summary

Uveal melanoma (UM) with an inflammatory phenotype, characterized by infiltrating leukocytes and increased human leukocyte antigen (HLA) expression, carry an increased risk of death due to metastases. These tumors should be ideal for T-cell based therapies, yet it is not clear why prognostically-infaust tumors have a high HLA expression. We set out to determine whether the level of HLA molecules in UM is associated with other genetic factors, HLA transcriptional regulators, or microenvironmental factors.