

Année de publication : 2021

Marcel Virginie, Kielbassa Janice, Marchand Virginie, Natchiar Kundhavai S, Paraqindes Hermes, Nguyen Van Long Flora, Ayadi Lilia, Bourguignon-Igel Valérie, Lo Monaco Piero, Monchiet Déborah, Scott Véronique, Tonon Laurie, E Bray Susan, Diot Alexandra, B Jordan Lee, M Thompson Alastair, Bourdon Jean-Christophe, Dubois Thierry, André Fabrice, Catez Frédéric, Puisieux Alain, Motorin Yuri, P Klaholz Bruno, Viari Alain, Diaz Jean-Jacques (2021 Feb 22)

Ribosomal RNA 2' O-methylation as a novel layer of inter-tumour heterogeneity in breast cancer

NAR Cancer : 3 : zcab006

Résumé

Samyuktha Suresh, Solène Huard, Thierry Dubois (2021 Jan 24)

CARM1/PRMT4: Making Its Mark beyond Its Function as a Transcriptional Coactivator.

Trends in cell biology : [DOI : 10.1016/j.tcb.2020.12.010](https://doi.org/10.1016/j.tcb.2020.12.010)

Résumé

Coactivator-associated arginine methyltransferase 1 (CARM1), identified 20 years ago as a coregulator of transcription, is an enzyme that catalyzes arginine methylation of proteins. Beyond its well-established involvement in the regulation of transcription, the physiological functions of CARM1 are still poorly understood. However, recent studies have revealed novel roles of CARM1 in autophagy, metabolism, paraspeckles, and early development. In addition, CARM1 is emerging as an attractive therapeutic target and a drug response biomarker for certain types of cancer. Here, we provide a comprehensive overview of the structure of CARM1 and its post-translational modifications, its various functions, apart from transcriptional coactivation, and its involvement in cancer.

Année de publication : 2020

Didier Meseure, Sophie Vacher, Sabah Boudjemaa, Marick Laé, André Nicolas, Renaud Leclere, Walid Chemlali, Gabriel Champenois, Anne Schnitzler, Laetitia Lesage, Thierry Dubois, Ivan Bieche (2020 Oct 3)

Biopathological Significance of PIWI-piRNA Pathway Deregulation in Invasive Breast Carcinomas.

Cancers : [DOI : 10.3390/cancers12102833](https://doi.org/10.3390/cancers12102833)

Résumé

The PIWI proteins emerging in the development of human cancers, edify PIWI-piRNA

ribonucleoproteic complexes acting as pivotal regulators of genome integrity, differentiation and homeostasis. The aim of this study is to analyze the four PIWILs gene expression in invasive breast carcinomas (IBCs): at RNA level using quantitative RT-PCR (= 526) and protein level using immunohistochemistry (= 150). In normal breast tissue, PIWILs 2 and 4 were solely expressed, whereas an abnormal emergence of PIWIL1 and 3 was observed in respectively 30% and 6% of IBCs. Conversely, PIWIL2 was underexpressed in 48.3% and PIWIL4 downregulated in 43.3% of IBCs. Significant positive associations were observed between PIWIL4 underexpression, HR+ status and HR+ ERBB2+ molecular subtype and PIWIL2 underexpression, PR- status, ERBB2- status and molecular subtype. Similar patterns of PIWIL deregulation were observed in a multitumoral panel, suggesting a generic mechanism in most cancers. PIWIL2-4 underexpression was mainly regulated at epigenetic or post-transcriptional levels. PIWIL2 underexpression was significantly associated with DNA methylation and strong cytotoxic immune response. PIWIL2-4 were mainly associated with genes implicated in cell proliferation. As a result of this study, characterization of the PIWIL-piRNA pathway in IBCs opens interesting therapeutic perspectives using piRNAs, hypomethylating drugs, checkpoints immunotherapies and anti-PIWIL 1-3 antibodies.

Lamyae El Khalki, Virginie Maire, Thierry Dubois, Abdelmajid Zyad (2020 Jan 30)

Berberine Impairs the Survival of Triple Negative Breast Cancer Cells: Cellular and Molecular Analyses.

Molecules (Basel, Switzerland) : [DOI : 10.3390/molecules25030506](https://doi.org/10.3390/molecules25030506)

Résumé

Triple negative breast cancer (TNBC) is an aggressive breast cancer subtype. Non-available targeted therapy for TNBC represents its biggest treatment challenge. Thus, finding new promising effective drugs is urgently needed. In the present study, we investigated how berberine, a natural isoquinoline, impairs the survival of TNBC cells in both cellular and molecular levels. Our experimental model was based on the use of eight TNBC cell lines: MDA-MB-468, MDA-MB-231, HCC70, HCC38, HCC1937, HCC1143, BT-20, and BT-549. Berberine was cytotoxic against all treated TNBC cell lines. The most sensitive cell lines were HCC70 (IC = 0.19 μ M), BT-20 (IC = 0.23 μ M) and MDA-MB-468 (IC = 0.48 μ M). Using flow cytometry techniques, berberine, at 0.5 and 1 μ M for 120 and 144 h, not only induced cell cycle arrest, at G1 and/or G2/M phases, but it also triggered significant apoptosis. At the molecular level, these results are consistent with the expression of their related proteins using Western blot assays. Interestingly, while berberine was cytotoxic against TNBC cells, it had no effect on the viability of normal human breast cells MCF10A cultured in a 3D matrigel model. These results suggest that berberine may be a good potential candidate for TNBC drug development.

Olivier Zajac, Renaud Leclere, André Nicolas, Didier Meseure, Caterina Marchiò, Anne Vincent-Salomon, Sergio Roman-Roman, Marie Schoumacher, Thierry Dubois (2020 Jan 23)

AXL Controls Directed Migration of Mesenchymal Triple-Negative Breast Cancer

Cells.

Cells : [DOI : 10.3390/cells9010247](https://doi.org/10.3390/cells9010247)

Résumé

Triple-negative breast cancer (TNBC) is an aggressive form of breast cancer with high risk of relapse and metastasis. TNBC is a heterogeneous disease comprising different molecular subtypes including those with mesenchymal features. The tyrosine kinase AXL is expressed in mesenchymal cells and plays a role in drug resistance, migration and metastasis. We confirm that AXL is more expressed in mesenchymal TNBC cells compared to luminal breast cancer cells, and that its invalidation impairs cell migration while having no or little effect on cell viability. Here, we found that AXL controls directed migration. We observed that AXL displays a polarized localization at the Golgi apparatus and the leading edge of migratory mesenchymal TNBC cells. AXL co-localizes with F-actin at the front of the cells. In migratory polarized cells, the specific AXL inhibitor R428 displaces AXL and F-actin from the leading edge to a lateral area localized between the front and the rear of the cells where both are enriched in protrusions. In addition, R428 treatment disrupts the polarized localization of the Golgi apparatus towards the leading edge in migratory cells. Immunohistochemical analysis of aggressive chemo-resistant TNBC samples obtained before treatment reveals inter- and intra-tumor heterogeneity of the percentage of AXL expressing tumor cells, and a preference of these cells to be in contact with the stroma. Taken together, our study demonstrates that AXL controls directed cell migration most likely by regulating cell polarity.

Année de publication : 2019

Mathilde Vinet, Samyuktha Suresh, Virginie Maire, Clarisse Monchecourt, Fariba Némati, Laetitia Lesage, Fabienne Pierre, Mengliang Ye, Auriane Lescure, Amélie Brisson, Didier Meseure, André Nicolas, Guillem Rigai, Elisabetta Marangoni, Elaine Del Nery, Sergio Roman-Roman, Thierry Dubois (2019 Apr 9)

Protein arginine methyltransferase 5: A novel therapeutic target for triple-negative breast cancers.

Cancer medicine : 2414-2428 : [DOI : 10.1002/cam4.2114](https://doi.org/10.1002/cam4.2114)

Résumé

TNBC is a highly heterogeneous and aggressive breast cancer subtype associated with high relapse rates, and for which no targeted therapy yet exists. Protein arginine methyltransferase 5 (PRMT5), an enzyme which catalyzes the methylation of arginines on histone and non-histone proteins, has recently emerged as a putative target for cancer therapy. Potent and specific PRMT5 inhibitors have been developed, but the therapeutic efficacy of PRMT5 targeting in TNBC has not yet been demonstrated. Here, we examine the expression of PRMT5 in a human breast cancer cohort obtained from the Institut Curie, and evaluate the therapeutic potential of pharmacological inhibition of PRMT5 in TNBC. We find that PRMT5 mRNA and protein are expressed at comparable levels in TNBC, luminal breast tumors, and healthy mammary tissues. However, immunohistochemistry analyses reveal

that PRMT5 is differentially localized in TNBC compared to other breast cancer subtypes and to normal breast tissues. PRMT5 is heterogeneously expressed in TNBC and high PRMT5 expression correlates with poor prognosis within this breast cancer subtype. Using the small-molecule inhibitor EPZ015666, we show that PRMT5 inhibition impairs cell proliferation in a subset of TNBC cell lines. PRMT5 inhibition triggers apoptosis, regulates cell cycle progression and decreases mammosphere formation. Furthermore, EPZ015666 administration to a patient-derived xenograft model of TNBC significantly deters tumor progression. Finally, we reveal potentiation between EGFR and PRMT5 targeting, suggestive of a beneficial combination therapy. Our findings highlight a distinctive subcellular localization of PRMT5 in TNBC, and uphold PRMT5 targeting, alone or in combination, as a relevant treatment strategy for a subset of TNBC.

Laura Cantini, Gloria Bertoli, Claudia Cava, Thierry Dubois, Andrei Zinovyev, Michele Caselle, Isabella Castiglioni, Emmanuel Barillot, Loredana Martignetti (2019 Jan 19)

Identification of microRNA clusters cooperatively acting on epithelial to mesenchymal transition in triple negative breast cancer.

Nucleic acids research : 2205-2215 : [DOI : 10.1093/nar/gkz016](https://doi.org/10.1093/nar/gkz016)

Résumé

MicroRNAs play important roles in many biological processes. Their aberrant expression can have oncogenic or tumor suppressor function directly participating to carcinogenesis, malignant transformation, invasiveness and metastasis. Indeed, miRNA profiles can distinguish not only between normal and cancerous tissue but they can also successfully classify different subtypes of a particular cancer. Here, we focus on a particular class of transcripts encoding polycistronic miRNA genes that yields multiple miRNA components. We describe 'clustered miRNA Master Regulator Analysis (ClustMMRA)', a fully redesigned release of the MMRA computational pipeline (miRNA Master Regulator Analysis), developed to search for clustered miRNAs potentially driving cancer molecular subtyping. Genomically clustered miRNAs are frequently co-expressed to target different components of pro-tumorigenic signaling pathways. By applying ClustMMRA to breast cancer patient data, we identified key miRNA clusters driving the phenotype of different tumor subgroups. The pipeline was applied to two independent breast cancer datasets, providing statistically concordant results between the two analyses. We validated in cell lines the miR-199/miR-214 as a novel cluster of miRNAs promoting the triple negative breast cancer (TNBC) phenotype through its control of proliferation and EMT.

Année de publication : 2018

Virginie Maire, Faisal Mahmood, Guillem Rigauill, Mengliang Ye, Amélie Brisson, Fariba Némati, David Gentien, Gordon C Tucker, Sergio Roman-Roman, Thierry Dubois (2018 Dec 22)

LRP8 is overexpressed in estrogen-negative breast cancers and a potential target for these tumors.

Cancer medicine : 325-336 : [DOI : 10.1002/cam4.1923](https://doi.org/10.1002/cam4.1923)

Résumé

Triple-negative breast cancer (TNBC) is the breast cancer subtype with the worst prognosis. New treatments improving the survival of TNBC patients are, therefore, urgently required. We performed a transcriptome microarray analysis to identify new treatment targets for TNBC. We found that low-density lipoprotein receptor-related protein 8 (LRP8) was more strongly expressed in estrogen receptor-negative breast tumors, including TNBCs and those overexpressing HER2, than in luminal breast tumors and normal breast tissues. LRP8 depletion decreased cell proliferation more efficiently in estrogen receptor-negative breast cancer cell lines: TNBC and HER2 overexpressing cell lines. We next focused on TNBC cells for which targeted therapies are not available. LRP8 depletion induced an arrest of the cell cycle progression in G1 phase and programmed cell death. We also found that LRP8 is required for anchorage-independent growth in vitro, and that its depletion in vivo slowed tumor growth in a xenograft model. Our findings suggest that new approaches targeting LRP8 may constitute promising treatments for hormone-negative breast cancers, those overexpressing HER2 and TNBCs.

Sylvie Rodrigues-Ferreira, Anne Nehlig, Clarisse Monchecourt, Sarah Nasr, Laetitia Fuhrmann, Magali Lacroix-Triki, Ingrid Garberis, Véronique Scott, Suzette Delalogue, Barbara Pistilli, Philippe Vielh, Thierry Dubois, Anne Vincent-Salomon, Fabrice André, Clara Nahmias (2018 Oct 29)

Combinatorial expression of microtubule-associated EB1 and ATIP3 biomarkers improves breast cancer prognosis.

Breast cancer research and treatment : 573-583 : [DOI : 10.1007/s10549-018-5026-1](https://doi.org/10.1007/s10549-018-5026-1)

Résumé

The identification of molecular biomarkers for classification of breast cancer is needed to better stratify the patients and guide therapeutic decisions. The aim of this study was to investigate the value of MAPRE1 gene encoding microtubule-end binding proteins EB1 as a biomarker in breast cancer and evaluate whether combinatorial expression of MAPRE1 and MTUS1 gene encoding EB1-negative regulator ATIP3 may improve breast cancer diagnosis and prognosis.

Flora Nguyen Van Long, Audrey Lardy-Cleaud, Susan Bray, Sylvie Chabaud, Thierry Dubois, Alexandra Diot, Alastair M Thompson, Jean-Christophe Bourdon, David Perol, Philippe Bouvet, Jean-Jacques Diaz, Virginie Marcel (2018 Oct 27)

Druggable Nucleolin Identifies Breast Tumours Associated with Poor Prognosis That Exhibit Different Biological Processes.

Cancers : [DOI : E390](https://doi.org/10.3390/cancers10101730)

Résumé

Nucleolin (NCL) is a multifunctional protein with oncogenic properties. Anti-NCL drugs show

strong cytotoxic effects, including in triple-negative breast cancer (TNBC) models, and are currently being evaluated in phase II clinical trials. However, few studies have investigated the clinical value of and whether stratified cancer patients. Here, we have investigated for the first time the association of with clinical characteristics in breast cancers independently of the different subtypes. Using two independent series ($n = 216$; $n = 661$), we evaluated the prognostic value of in non-metastatic breast cancers using univariate and/or multivariate Cox-regression analyses. We reported that mRNA expression levels are markers of poor survivals independently of tumour size and lymph node invasion status ($n = 216$). In addition, an association of expression levels with poor survival was observed in TNBC ($n = 40$, overall survival (OS) = 0.0287, disease-free survival (DFS) = 0.0194). Transcriptomic analyses issued from The Cancer Genome Atlas (TCGA) database ($n = 661$) revealed that breast tumours expressing either low or high mRNA expression levels exhibit different gene expression profiles. These data suggest that tumours expressing high mRNA levels are different from those expressing low mRNA levels. is an independent marker of prognosis in breast cancers. We anticipated that anti-NCL is a promising therapeutic strategy that could rapidly be evaluated in high -expressing tumours to improve breast cancer management.

Alessia Castagnino, Antonio Castro-Castro, Marie Irondelle, Alan Guichard, Catalina Lodillinsky, Laetitia Fuhrmann, Sophie Vacher, Sonia Agüera-González, Anna Zagryazhskaya-Masson, Maryse Romao, Carole El Kesrouani, Angelika A Noegel, Thierry Dubois, Graça Raposo, James E Bear, Christoph S Clemen, Anne Vincent-Salomon, Ivan Bièche, Philippe Chavrier (2018 Aug 2)

Coronin 1C promotes triple-negative breast cancer invasiveness through regulation of MT1-MMP traffic and invadopodia function.

Oncogene : 6425-6441 : DOI : [10.1038/s41388-018-0422-x](https://doi.org/10.1038/s41388-018-0422-x)

Résumé

Membrane type 1-matrix metalloproteinase (MT1-MMP), a membrane-tethered protease, is key for matrix breakdown during cancer invasion and metastasis. Assembly of branched actin networks by the Arp2/3 complex is required for MT1-MMP traffic and formation of matrix-degradative invadopodia. Contrasting with the well-established role of actin filament branching factor cortactin in invadopodia function during cancer cell invasion, the contribution of coronin-family debranching factors to invadopodia-based matrix remodeling is not known. Here, we investigated the contribution of coronin 1C to the invasive potential of breast cancer cells. We report that expression of coronin 1C is elevated in invasive human breast cancers, correlates positively with MT1-MMP expression in relation with increased metastatic risk and is a new independent prognostic factor in breast cancer. We provide evidence that, akin to cortactin, coronin 1C is required for invadopodia formation and matrix degradation by breast cancer cells lines and for 3D collagen invasion by multicellular spheroids. Using intravital imaging of orthotopic human breast tumor xenografts, we find that coronin 1C accumulates in structures forming in association with collagen fibrils in the tumor microenvironment. Moreover, we establish the role of coronin 1C in the regulation of positioning and trafficking of MT1-MMP-positive endolysosomes. These results identify coronin 1C as a novel player of the multi-faceted mechanism responsible for invadopodia formation, MT1-MMP surface exposure and invasiveness in breast cancer cells.

Sylvie Maubant, Tania Tahtouh, Amélie Brisson, Virginie Maire, Fariba Némati, Bruno Tesson, Mengliang Ye, Guillem Rigall, Maité Noizet, Aurélie Dumont, David Gentien, Bérengère Marty-Prouvost, Leanne de Koning, Sardar Faisal Mahmood, Didier Decaudin, Francisco Cruzalegui, Gordon C Tucker, Sergio Roman-Roman, Thierry Dubois (2018 Jun 2)

LRP5 regulates the expression of STK40, a new potential target in triple-negative breast cancers.

Oncotarget : 22586-22604 : [DOI : 10.18632/oncotarget.25187](https://doi.org/10.18632/oncotarget.25187)

Résumé

Triple-negative breast cancers (TNBCs) account for a large proportion of breast cancer deaths, due to the high rate of recurrence from residual, resistant tumor cells. New treatments are needed, to bypass chemoresistance and improve survival. The WNT pathway, which is activated in TNBCs, has been identified as an attractive pathway for treatment targeting. We analyzed expression of the WNT coreceptors LRP5 and LRP6 in human breast cancer samples. As previously described, LRP6 was overexpressed in TNBCs. However, we also showed, for the first time, that LRP5 was overexpressed in TNBCs too. The knockdown of LRP5 or LRP6 decreased tumorigenesis and , identifying both receptors as potential treatment targets in TNBC. The apoptotic effect of LRP5 knockdown was more robust than that of LRP6 depletion. We analyzed and compared the transcriptomes of cells depleted of LRP5 or LRP6, to identify genes specifically deregulated by LRP5 potentially implicated in cell death. We identified serine/threonine kinase 40 (STK40) as one of two genes specifically downregulated soon after LRP5 depletion. STK40 was found to be overexpressed in TNBCs, relative to other breast cancer subtypes, and in various other tumor types. STK40 depletion decreased cell viability and colony formation, and induced the apoptosis of TNBC cells. In addition, STK40 knockdown impaired growth in an anchorage-independent manner and slowed tumor growth . These findings identify the largely uncharacterized putative protein kinase STK40 as a novel candidate treatment target for TNBC.

Année de publication : 2017

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](https://doi.org/10.1038/bjc.2017.131)

Résumé

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).

Bo Li, Triona Ni Chonghaile, Yue Fan, Stephen F Madden, Rut Klinger, Aisling E O'Connor, Louise Walsh, Gillian O'Hurley, Girish Mallya Udipi, Jesuchristopher Joseph, Finbarr Tarrant, Emer Conroy, Alexander Gaber, Suet-Feung Chin, Helen A Bardwell, Elena Provenzano, John Crown, Thierry Dubois, Sabine Linn, Karin Jirstrom, Carlos Caldas, Darran P O'Connor, William M Gallagher (2017 Apr 30)

Therapeutic Rationale to Target Highly Expressed CDK7 Conferring Poor Outcomes in Triple-Negative Breast Cancer.

Cancer research : 3834-3845 : [DOI : 10.1158/0008-5472.CAN-16-2546](https://doi.org/10.1158/0008-5472.CAN-16-2546)

Résumé

Triple-negative breast cancer (TNBC) patients commonly exhibit poor prognosis and high relapse after treatment, but there remains a lack of biomarkers and effective targeted therapies for this disease. Here, we report evidence highlighting the cell-cycle-related kinase CDK7 as a driver and candidate therapeutic target in TNBC. Using publicly available transcriptomic data from a collated set of TNBC patients (= 383) and the METABRIC TNBC dataset (= 217), we found mRNA levels to be correlated with patient prognosis. High CDK7 protein expression was associated with poor prognosis within the RATHER TNBC cohort (= 109) and the METABRIC TNBC cohort (= 203). The highly specific CDK7 kinase inhibitors, BS-181 and THZ1, each downregulated CDK7-mediated phosphorylation of RNA polymerase II, indicative of transcriptional inhibition, with THZ1 exhibiting 500-fold greater potency than BS-181. Mechanistic investigations revealed that the survival of MDA-MB-231 TNBC cells relied heavily on the BCL-2/BCL-XL signaling axes in cells. Accordingly, we found that combining the BCL-2/BCL-XL inhibitors ABT-263/ABT199 with the CDK7 inhibitor THZ1 synergized in producing growth inhibition and apoptosis of human TNBC cells. Collectively, our results highlight elevated CDK7 expression as a candidate biomarker of poor prognosis in TNBC, and they offer a preclinical proof of concept for combining CDK7 and BCL-2/BCL-XL inhibitors as a mechanism-based therapeutic strategy to improve TNBC treatment. .

Année de publication : 2016

Tina Grusso, Virginie Mieulet, Melissa Cardon, Brigitte Bourachot, Yann Kieffer, Flavien Devun, Thierry Dubois, Marie Dutreix, Anne Vincent-Salomon, Kyle Malcolm Miller, Fatima Mechta-Grigoriou (2016 Mar 24)

Chronic oxidative stress promotes H2AX protein degradation and enhances chemosensitivity in breast cancer patients.

EMBO molecular medicine : 527-49 : [DOI : 10.15252/emmm.201505891](https://doi.org/10.15252/emmm.201505891)

Résumé

Anti-cancer drugs often increase reactive oxygen species (ROS) and cause DNA damage. Here, we highlight a new cross talk between chronic oxidative stress and the histone variant H2AX, a key player in DNA repair. We observe that persistent accumulation of ROS, due to a deficient JunD-/Nrf2-antioxidant response, reduces H2AX protein levels. This effect is

mediated by an enhanced interaction of H2AX with the E3 ubiquitin ligase RNF168, which is associated with H2AX poly-ubiquitination and promotes its degradation by the proteasome. ROS-mediated H2AX decrease plays a crucial role in chemosensitivity. Indeed, cycles of chemotherapy that sustainably increase ROS reduce H2AX protein levels in Triple-Negative breast cancer (TNBC) patients. H2AX decrease by such treatment is associated with an impaired NRF2-antioxidant response and is indicative of the therapeutic efficiency and survival of TNBC patients. Thus, our data describe a novel ROS-mediated regulation of H2AX turnover, which provides new insights into genetic instability and treatment efficacy in TNBC patients.