Publications
Breast Cancer Biology

Year of publication 2021

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

*NAR Cancer* : 3 : zcab006

**Summary**

Year of publication 2019


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

*Cancer medicine* : 2414-2428 : [DOI: 10.1002/cam4.2114]

**Summary**

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.

**Year of publication 2018**


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


**Summary**

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.


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

*Cancers* : [DOI: E390]

**Summary**

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 ( = 216; = 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 ($= 216$). In addition, an association of expression levels with poor survival was observed in TNBC ($= 40$, overall survival (OS) = 0.0287, disease-free survival (DFS) = 0.0194). Transcriptomic analyses issued from The Cancer Genome Atlas (TCGA) database ($= 661$) 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.


**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)

**Summary**

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.

Year of publication 2013

Sophie Broutin, Frédéric Commo, Leanne De Koning, Bérengère Marty-Prouvost, Ludovic Lacroix, Monique Talbot, Bernard Caillou, Thierry Dubois, Anderson J Ryan, Corinne Dupuy, Martin
Schlumberger, Jean-Michel Bidart (2013 Nov 22)

**Changes in signaling pathways induced by vandetanib in a human medullary thyroid carcinoma model, as analyzed by reverse phase protein array.**

*Thyroid : official journal of the American Thyroid Association* : 43-51 : [DOI]: 10.1089/thy.2013.0514

**Summary**

Medullary thyroid carcinoma (MTC) is a rare tumor that is caused by activating mutations in the proto-oncogene RET. Vandetanib, a tyrosine-kinase inhibitor, has been recently approved to treat adult patients with metastatic MTC. The aim of this study was to investigate changes in signaling pathways induced by vandetanib treatment in preclinical MTC models, using the reverse-phase protein array method (RPPA).


**Hepatocyte-specific Dyrk1a gene transfer rescues plasma apolipoprotein A-I levels and aortic Akt/GSK3 pathways in hyperhomocysteinemic mice.**

*Biochimica et biophysica acta* : 718-28 : [DOI]: 10.1016/j.bbadis.2013.02.008

**Summary**

Hyperhomocysteinemia, characterized by high plasma homocysteine levels, is recognized as an independent risk factor for cardiovascular diseases. The increased synthesis of homocysteine, a product of methionine metabolism involving B vitamins, and its slower intracellular utilization cause increased flux into the blood. Plasma homocysteine level is an important reflection of hepatic methionine metabolism and the rate of processes modified by B vitamins as well as different enzyme activity. Lowering homocysteine might offer therapeutic benefits. However, approximately 50% of hyperhomocysteinemic patients due to cystathionine-beta-synthase deficiency are biochemically responsive to pharmacological doses of B vitamins. Therefore, effective treatments to reduce homocysteine levels are needed, and gene therapy could provide a novel approach. We recently showed that hepatic expression of DYRK1A, a serine/threonine kinase, is negatively correlated with plasma homocysteine levels in cystathionine-beta-synthase deficient mice, a mouse model of hyperhomocysteinemia. Therefore, Dyrk1a is a good candidate for gene therapy to normalize homocysteine levels. We then used an adenoviral construct designed to restrict expression of DYRK1A to hepatocytes, and found decreased plasma homocysteine levels after hepatocyte-specific Dyrk1a gene transfer in hyperhomocysteinemic mice. The elevation of pyridoxal phosphate was consistent with the increase in cystathionine-beta-synthase activity. Commensurate with the decreased plasma homocysteine levels, targeted hepatic expression of DYRK1A resulted in elevated plasma paraoxonase-1 activity and apolipoprotein A-I levels, and rescued the Akt/GSK3 signaling pathways in aorta of mice, which can prevent homocysteine-induced endothelial dysfunction. These results demonstrate that hepatocyte-restricted Dyrk1a gene transfer can offer a useful therapeutic targets for the development of
new selective homocysteine lowering therapy.