Year of publication 2016

Magali Michaut, Suet-Feung Chin, Ian Majewski, Tesa M Severson, Tycho Bismeijer, Leanne de Koning, Justine K Peeters, Philip C Schouten, Oscar M Rueda, Astrid J Bosma, Finbarr Tarrant, Yue Fan, Beilei He, Zheng Xue, Lorenza Mittempergher, Roelof J C Kluin, Jeroen Heijmans, Mireille Snel, Bernard Pereira, Andreas Schlicker, Elena Provenzano, Hamid Raza Ali, Alexander Gaber, Gillian O'Hurley, Sophie Lehn, Jettie J F Muris, Jelle Wesseling, Elaine Kay, Stephen John Sammut, Helen A Bardwell, Aurélie S Barbet, Floriane Bard, Caroline Lecerf, Darran P O'Connor, Daniël J Vis, Cyril H Benes, Ultan McDermott, Mathew J Garnett, Iris M Simon, Karin Jirström, Thierry Dubois, Sabine C Linn, William M Gallagher, Lodewyk F A Wessels, Carlos Caldas, Rene Bernards (2016 Jan 6)

Integration of genomic, transcriptomic and proteomic data identifies two biologically distinct subtypes of invasive lobular breast cancer.

Scientific reports : 18517 : DOI : 10.1038/srep18517

Summary

Invasive lobular carcinoma (ILC) is the second most frequently occurring histological breast cancer subtype after invasive ductal carcinoma (IDC), accounting for around 10% of all breast cancers. The molecular processes that drive the development of ILC are still largely unknown. We have performed a comprehensive genomic, transcriptomic and proteomic analysis of a large ILC patient cohort and present here an integrated molecular portrait of ILC. Mutations in CDH1 and in the PI3K pathway are the most frequent molecular alterations in ILC. We identified two main subtypes of ILCs: (i) an immune related subtype with mRNA up-regulation of PD-L1, PD-1 and CTLA-4 and greater sensitivity to DNA-damaging agents in representative cell line models; (ii) a hormone related subtype, associated with Epithelial to Mesenchymal Transition (EMT), and gain of chromosomes 1q and 8q and loss of chromosome 11q. Using the somatic mutation rate and eIF4B protein level, we identified three groups with different clinical outcomes, including a group with extremely good prognosis. We provide a comprehensive overview of the molecular alterations driving ILC and have explored links with therapy response. This molecular characterization may help to tailor treatment of ILC through the application of specific targeted, chemo- and/or immune-therapies.

Year of publication 2015

Céline Baldeyron, Amélie Brisson, Bruno Tesson, Fariba Némati, Stéphane Koundrioukoff, Elie Saliba, Leanne De Koning, Elise Martel, Mengliang Ye, Guillem Rigaill, Didier Meseure, André Nicolas, David Gentien, Didier Decaudin, Michelle Debatisse, Stéphane Depil, Francisco Cruzalegui, Alain Pierré, Sergio Roman-Roman, Gordon C Tucker, Thierry Dubois (2015 May 26)

TIPIN depletion leads to apoptosis in breast cancer cells.

Molecular oncology : 1580-98 : DOI : 10.1016/j.molonc.2015.04.010

Summary

Triple-negative breast cancer (TNBC) is the breast cancer subgroup with the most aggressive clinical behavior. Alternatives to conventional chemotherapy are required to improve the survival of TNBC patients. Gene-expression analyses for different breast cancer subtypes revealed significant overexpression of the Timeless-interacting protein (TIPIN), which is involved in the stability of DNA replication forks, in the highly proliferative associated TNBC samples. Immunohistochemistry analysis showed higher expression of TIPIN in the most proliferative and aggressive breast cancer subtypes including TNBC, and no TIPIN expression in healthy breast tissues. The depletion of TIPIN by RNA interference impairs the proliferation of both human breast cancer and non-tumorigenic cell lines. However, this effect may be specifically associated with apoptosis in breast cancer cells. TIPIN silencing results in higher levels of single-stranded DNA (ssDNA), indicative of replicative stress (RS), in TNBC compared to non-tumorigenic cells. Upon TIPIN depletion, the speed of DNA replication fork was significantly decreased in all BC cells. However, TIPIN-depleted TNBC cells are unable to fire additional replication origins in response to RS and therefore undergo apoptosis. TIPIN knockdown in TNBC cells decreases tumorigenicity in vitro and delays tumor growth in vivo. Our findings suggest that TIPIN is important for the maintenance of DNA replication and represents a potential treatment target for the worst prognosis associated breast cancers, such as TNBC.

S Rondeau, S Vacher, L De Koning, A Briaux, A Schnitzler, W Chemlali, C Callens, R Lidereau, I Bièche (2015 Mar 6)

ATM has a major role in the double-strand break repair pathway dysregulation in sporadic breast carcinomas and is an independent prognostic marker at both mRNA and protein levels.

British journal of cancer : 1059-66 : DOI : 10.1038/bjc.2015.60

Summary

Ataxia telangiectasia mutated (ATM) is a kinase that has a central role in the maintenance of genomic integrity by activating cell cycle checkpoints and promoting repair of DNA double-strand breaks (DSB). In breast cancer, a low level of ATM was correlated with poor outcome; however, the molecular mechanism of this downregulation is still unclear.