CANCER DE MAMA

MYC and MCL1 Cooperatively Promote Chemotherapy-Resistant Breast Cancer Stem Cells via Regulation of Mitochondrial Oxidative Phosphorylation.

Lee KM, Giltnane JM, Balko JM, Schwarz LJ, Guerrero-Zotano AL, Hutchinson KE, Nixon MJ, Estrada MV, Sánchez V, Sanders ME, Lee T, Gómez H, Lluch A, Pérez-Fidalgo JA, Wolf MM, Andrejeva G, Rathmell JC, Fesik SW, Arteaga CL.

Cell Metab. 2017 Oct 3;26(4):633-647.e7.

Abstract

Most patients with advanced triple-negative breast cancer (TNBC) develop drug resistance. MYC and MCL1 are frequently co-amplified in drug-resistant TNBC after neoadjuvant chemotherapy. Herein, we demonstrate that MYC and MCL1 cooperate in the maintenance of chemotherapy-resistant cancer stem cells (CSCs) in TNBC. MYC and MCL1 increased mitochondrial oxidative phosphorylation (mtOXPHOS) and the generation of reactive oxygen species (ROS), processes involved in maintenance of CSCs. A mutant of MCL1 that cannot localize in mitochondria reduced mtOXPHOS, ROS levels, and drug-resistant CSCs without affecting the anti-apoptotic function of MCL1. Increased levels of ROS, a by-product of activated mtOXPHOS, led to the accumulation of HIF-1α. Pharmacological inhibition of HIF-1α attenuated CSC enrichment and tumor initiation in vivo. These data suggest that (1) MYC and MCL1 confer resistance to chemotherapy by expanding CSCs via mtOXPHOS and (2) targeting mitochondrial respiration and HIF-1α may reverse chemotherapy resistance in TNBC.

Update on tumor-infiltrating lymphocytes (TILs) in breast cancer, including recommendations to assess TILs in residual disease after neoadjuvant therapy and in carcinoma in situ: a report of the International Immuno-Oncology Biomarker Working Group on Breast Cancer.

Dieci MV, Radosevic-Robin N, Fineberg S, van den Eynden G, Ternes N, Penault-Llorca F, Pruneri G, D'Alfonso TM, Demaria S, Castaneda C, Sanchez J, Badve S, Michiels S, Bossuyt V, Rojo F, Singh B, Nielsen T, Viale G, Kim SR, Hewitt S, Wienert S, Loibl S, Rimm D, Symmans F, Denkert C, Adams S, Loi S, Salgado R; International Immuno-Oncology Biomarker Working Group on Breast Cancer.

Semin Cancer Biol. 2017 Oct 9. pii: S1044-579X(17)30217-1.

Abstract

Morphological evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer is gaining momentum as evidence strengthens the clinical relevance of this immunological biomarker. TILs in the post-neoadjuvant residual disease setting are acquiring increasing importance as a stratifying marker in clinical trials, considering the raising interest on immunotherapeutic strategies after neoadjuvant chemotherapy. TILs in ductal carcinoma in situ, with or without invasive carcinoma, represent an emerging area of clinical breast cancer research. The aim of this report is to update pathologists, clinicians and researchers on TIL assessment in both the post-neoadjuvant residual disease and the ductal carcinoma in situ settings. The International Immuno-Oncology Working Group proposes a method for assessing TILs in these settings, based on the previously published International Guidelines on TIL Assessment in Breast Cancer. In this regard, these recommendations represent a consensus guidance for pathologists, aimed to achieve the highest possible consistency among future studies.

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Epidemiology and pathophysiology of pregnancy-associated breast cancer: A review.

Ruiz R, Herrero C, Strasser-Weippl K, Touya D, St Louis J, Bukowski A, Goss PE.

Breast. 2017 Oct;35:136-141.

Abstract

The interactions between pregnancy and breast cancer (BC) are complex. Overall, parity is associated with long-term protective effects against BC, however in a small group of susceptible patients, pregnancy can lead to the development of a form of BC with a particularly poor prognosis. Pregnancy-associated breast cancer (PABC) remains an under-studied but important and growing clinical problem worldwide. Several aspects of PABC, including risk factors and mechanisms involved in its occurrence and aggressiveness, are incompletely understood. This review aims to summarize the epidemiology, biology, patho-physiology and clinical characteristics of PABC. We emphasize that age at first pregnancy, absence of breastfeeding and family history stand out as possible risk factors for developing PABC that ought to be incorporated into clinical tools for assessing a woman's risk of developing PABC. Also, improved methods for identifying women at risk of developing PABC in the general population are needed.

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Expressed Gene Fusions as Frequent Drivers of Poor Outcomes in Hormone Receptor Positive Breast Cancer.

Matissek KJ, Onozato ML, Sun S, Zheng Z, Schultz A, Lee J, Patel K, Jerevall PL, Saladi SV, MacLeay A, Tavallai M, Badovinac-Crnjevic T, Barrios C, Beşe N, Chan A, Chavarri-Guerra Y, Debiasi M, Demirdogen E, Egeli U, Gökgöz S, Gomez H, Liedke P, Tasdelen I, Tolunay S, Werutsky G, St Louis J, Horick N, Finkelstein DM, Le LP, Bardia A, Goss PE, Sgroi DC, Iafrate AJ, Ellisen LW.

Cancer Discov. 2017 Dec 14. pii: CD-17-0535.

Abstract

We sought to uncover novel genetic drivers of hormone-receptor positive (HR+) breast cancer, employing a targeted next-generation sequencing approach for detecting expressed gene rearrangements without prior knowledge of the fusion partners. We identified intergenic fusions involving driver genes including PIK3CA, AKT3, RAF1 and ESR1 in 14% (24/173) of unselected patients with advanced HR+ breast cancer. Fluorescence in situ hybridization (FISH) confirmed the corresponding chromosomal rearrangements in both primary and metastatic tumors. Expression of novel kinase fusions in non-transformed cells deregulates phosphoprotein signaling, cell proliferation and survival in 3-dimensional culture, while expression in HR+ breast cancer models modulates estrogen-dependent growth and confers hormonal therapy resistance in vitro and in vivo. Strikingly, shorter overall survival was observed in patients with rearrangement-positive versus -negative tumors. Correspondingly, fusions were uncommon (<5%) among 300 patients presenting with primary HR+ breast cancer. Collectively, our findings identify expressed gene fusions as frequent and potentially actionable drivers in HR+ breast cancer.

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Metronomic chemotherapy for non-metastatic triple negative breast cancer: Selection is the key.

Rabanal C, Ruiz R, Neciosup S, Gomez H.

World J Clin Oncol. 2017 Dec 10;8(6):437-446.

Abstract

Triple negative breast cancer (TNBC) accounts for 15%-20% of all breast cancer, and is still defined as what it is not. Currently, TNBC is the only type of breast cancer for which there are no approved targeted therapies and maximum tolerated dose chemotherapy with taxanes and anthracycline-containing regimens is still the standard of care in both the neoadjuvant and adjuvant settings. In the last years, metronomic chemotherapy (MC) is being explored as an alternative to improve outcomes in TNBC. In the neoadjuvant setting, purely metronomic and hybrid approaches have been developed with the objective of increasing complete pathologic response (pCR) and prolonging disease free survival. These regimens proved to be very effective achieving pCR rates between 47%-60%, but at the cost of great toxicity. In the adjuvant setting, MC is used to intensify adjuvant chemotherapy and, more promisingly, as maintenance therapy for high-risk patients, especially those with no pCR after neoadjuvant chemotherapy. Considering the dismal prognosis of TNBC, any strategy that potentially improves outcomes, specially being the oral agents broadly available and inexpensive, should be considered and certainly warrants further exploration. Finally, the benefit of MC needs to be validated in properly designed clinical trials were the selection of the population is the key.

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