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Review

Drug resistance to targeted therapies: Déjà vu all over again

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ABSTRACT

A major limitation of targeted anticancer therapies is intrinsic or acquired resistance. This review emphasizes similarities in the mechanisms of resistance to endocrine therapies in breast cancer and those seen with the new generation of targeted cancer therapeutics. Resistance to single-agent cancer therapeutics is frequently the result of reactivation of the signaling pathway, indicating that a major limitation of targeted agents lies in their inability to fully block the cancer-relevant signaling pathway. The development of mechanism-based combinations of targeted therapies together with non-invasive molecular disease monitoring is a logical way forward to delay and ultimately overcome drug resistance development.

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1. Introduction

Resistance to therapy remains a major challenge in oncology. Resistance comes in two flavors: (1) early intrinsic resistance (also known as innate or *de novo* resistance) or fast adaptive tumor responses, and (2) late acquired resistance, resulting from clonal evolution of resistant variants. Anticancer drug resistance has been studied since the 1960s (Brockman,

Abbreviations: aCGH, array comparative genomic hybridization; ALK, anaplastic lymphoma kinase; BCAR1, breast cancer anti-estrogen resistance 1; BCR-ABL, breakpoint cluster region protein – Abelson murine leukemia viral oncogene homolog 1; CML, chronic myeloid leukemia; RC, colorectal cancer; EGFR, epidermal growth factor receptor; EMT, epithelial-to-mesenchymal transition; ERα, estrogen receptor alpha; ESR1, estrogen receptor 1; FISH, fluorescent *in situ* hybridization; GBM, glioblastoma multiforme; GEMMs, genetically engineered mouse models; IGF1R, insulin-like growth factor 1 receptor; IHC, immunohistochemistry; MAPK, mitogen-activated protein kinase; MLPA, multiplex ligation-dependent probe amplification; NCOA3, nuclear receptor coactivatior 3; NSCLC, non-small cell lung cancer; ORF, open-reading frame; pCR, pathological complete response; PELP1, proline, glutamate and leucine rich protein 1; PDGFRB, beta-type platelet-derived growth factor receptor; PDX, patient-derived xenograft; PIK3CA, phosphatidylinositol 3-kinase catalytic subunit; PKA, protein kinase A; qPCR, quantitative polymerase chain reaction; ROS1, c-ros oncogene 1; RTK, receptor tyrosine kinases; SERM, selective estrogen receptor modulator; shRNA, short-hairpin RNA; SRC, v-src avian sarcoma viral oncogene homolog; TGFβ, transforming growth factor beta; TNBC, triple-negative breast cancer; TKI, tyrosine kinase inhibitor.

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1963), but has gained momentum after the introduction of targeted cancer therapeutics and several technological advances such as RNA interference (Brummelkamp et al., 2002) and next generation DNA/RNA sequencing. Selective targeting of activated pathways has proven to be effective, but the observed responses are usually partial and not durable when using single agent therapies. This translates clinically in prolonged progression-free survival, but similar overall survival compared to standard of care. Examples where prolonged progression-free survival has been achieved without giving rise to improved overall survival are crizotinib (ALK-TKI) in advanced ALK-positive Non-Small Cell Lung Cancer (NSCLC) and gefitinib (EGFR-TKI) in *EGFR*-mutated NSCLC (Maemondo et al., 2010; Shaw et al., 2013). An exception is the case of the $BRAF^{V600E}$-specific inhibitor vemurafenib in $BRAF^{V600E}$-mutated metastatic melanoma. Patients with metastatic melanoma have a median survival of 6–10 months and activating *BRAF* mutation was associated with shortened survival in patients with metastatic disease (Long et al., 2011). A phase 3 trial with vemurafenib in $BRAF^{V600E}$-mutated metastatic melanoma showed significant improvement in both progression-free survival and overall survival with vemurafenib compared to chemotherapy in an early interim analysis of overall survival (Chapman et al., 2011). Although the median duration of follow-up in this study was too short to draw strong conclusions, long follow-up data of a phase 2 trial with vemurafenib in the same clinical setting confirmed these early results and showed increase in median overall survival to approximately 16 months (Sosman et al., 2012).

Here we review the recent insights into mechanisms of resistance to targeted therapies. We focus on the reactivation of signaling pathways as a recurrent pattern of resistance development to single-agent targeted therapies. We first discuss the resistance mechanisms to endocrine therapy in breast cancer, the first targeted therapy introduced in the clinic. We will use this as an example to highlight that the mechanisms of resistance to endocrine therapy that have been identified in breast cancer are seen all over again with the new pathways-targeted therapies in other cancers. Finally, we argue that synthetic lethal combinations of targeted therapies together with non-invasive molecular disease monitoring are a promising way forward to fight drug resistance.

2. Endocrine resistance in breast cancer

The synthesis of competitive inhibitors of the binding of the hormone estrogen to its receptor (ERα) in the 1970s led to the development of the first targeted cancer drug: tamoxifen. Tamoxifen is a triphenylethylene derivative classified as a selective estrogen receptor modulator (SERM). It impairs the mitogenic function of ERα in breast cancer by competing with estrogen for binding to the receptor. The binding of tamoxifen to the ERα changes the receptor conformation, which is distinct from the conformational change that is induced by estrogen binding. This conformation change prevents the formation of the ERα complex with its essential transcriptional co-activators and thereby inhibits ERα-mediated transcription (Shiau et al., 1998). A second class of endocrine drugs that target estrogen synthesis has been developed subsequently: the aromatase inhibitors. Aromatase is the enzyme responsible for the estrogen synthesis from androgenic substrates (extra-ovarian synthesis) (Smith and Dowsett, 2003). Aromatase inhibitors cannot inhibit the estradiol production in the ovaries themselves and are therefore not active in premenopausal patients without ovarian suppression. Consequently, tamoxifen is typically given to premenopausal patients, whereas aromatase inhibitors are given to postmenopausal patients, although postmenopausal sequential treatment of tamoxifen and aromatase inhibitors is often prescribed as well.

Almost 70% of breast cancers are classified as ERα-positive by IHC, and endocrine therapies targeting estrogen action (anti-estrogens and aromatase inhibitors) are only effective in ERα-positive breast cancers. Expression of ERα protein is strongly predictive of response to endocrine therapies (Davies et al., 2011). However, approximately one third of ERα-positive early breast cancers do not respond to endocrine therapy (intrinsic resistance) or relapse after an initial response (acquired resistance) (EBCTCG, 2005). The proportion of breast cancer patients with advanced or metastatic disease that relapses during or after endocrine therapy is even higher. It is important to note that patients who develop resistance to one kind of endocrine treatment can still respond to another type (Wang et al., 2009; Yoo et al., 2011). The various mechanisms underlying resistance to endocrine therapy that have been proposed and studied are outlined below. They can be classified in three main categories: (1) alterations of the drug target (i.e. *ESR1*/ERα), (2) alterations in downstream and upstream effectors of ERα signaling, and (3) bypass mechanisms (Table 1).

2.1. *Alterations of* ESR1 *and its encoded protein* ERα

Patients with the highest ERα protein expression benefit slightly more from tamoxifen compared to patients with low receptor expression, but the latter group still have substantial benefit (Davies et al., 2011). However, response to tamoxifen is rare in ERα-negative breast cancer. A portion of ERα-positive tumors becomes independent of estrogen signaling after which they loose ERα expression and, hence, are tamoxifen resistant. Gutierrez et al. studied the ERα expression in paired clinical breast cancer samples from before the start of tamoxifen treatment and after tumor progression (Gutierrez et al., 2005). They found loss of ERα expression in 17% of ERα-positive tumors at the time of tumor progression. This was in line with earlier reports showing that ERα loss occurs in 15–30% of the tumors at the time of recurrence (Encarnacion et al., 1993; Johnston et al., 1995; Kuukasjarvi et al., 1996). Loss of ERα was associated with tamoxifen resistance (Johnston et al., 1995) and can be used as a predictor of poor response to subsequent endocrine therapy (Kuukasjarvi et al., 1996).

Mutations in *ESR1*, the gene coding for ERα, were proposed as yet another possible mechanism of endocrine therapy resistance. However, *ESR1* mutations were only found in a very low percentage of primary breast cancers, if at all present (Cancer Genome Atlas Network, 2012). In a recent report by Li et al., *ESR1* ligand-binding domain mutations were identified

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