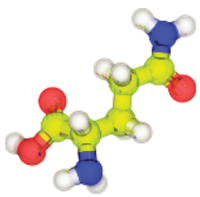
Breast Cancer

Major finding: Inhibition of the antiporter xCT depletes glutathione and decreases the growth of TNBC tumors.

Approach: Glutamine uptake and dependence were comprehensively assessed in a panel of breast cancer cells.

Impact: Glutamine auxotrophy in TNBC can be targeted by limiting glutamine uptake or utilization.

THE xCT ANTIPORTER IS A POTENTIAL THERAPEUTIC TARGET IN TNBC



Enhanced reliance on glucose or glutamine is a common feature of many tumors, suggesting inhibition of key metabolic enzymes as a therapeutic strategy. However, nutrient utilization in tumors is heterogeneous, and a comprehensive analysis of responses to metabolic perturbations in breast cancer is lacking, prompting Timmerman and colleagues to determine the gene expression profiles and nutrient dependencies of a large panel of breast cancer cell lines compared with those of nontumorigenic human mammary epithelial cells. Although glucose consumption was highest in luminal tumors, and triple-negative breast cancers (TNBC) consumed higher amounts of glutamine, nutrient dependencies varied widely. Glutamine restriction reduced the expansion rate of the majority of breast cancer cells but induced S-phase stalling in a subset of TNBC cell lines, which did not expand or underwent apoptosis in response to glutamine deprivation. Expression of genes that regulate glutamine metabolism was not sufficient to identify this subset of TNBC cells, and supplementation with alternative carbon sources was unable to rescue these cells from glutamine restriction, indicating that these cells are glutamine auxotrophs that cannot synthesize the required amount of this nutrient. These auxotrophic cell lines were sensitive to therapeutic agents that blocked glutamine access or inhibited glutamine-utilizing enzymes. In addition, glutamine restriction decreased cystine/glutamate exchange via solute carrier family 7 (anionic amino acid transporter light chain, xc- system), member 11 (SLC7A11, also known as xCT), which is required for synthesis of the antioxidant glutathione and was upregulated in TNBC cells. Depletion or pharmacologic inhibition of xCT reduced glutathione levels, increased intracellular reactive oxygen species, diminished the growth of auxotrophic TNBC xenografts, and enhanced the sensitivity of TNBC cells to carboplatin. These findings provide insight into the metabolic activities of breast cancer cells and identify xCT as a potential therapeutic target in TNBC. ■

Timmerman LA, Holton T, Yuneva M, Louie RJ, Padró M, Daemen A, et al. Glutamine sensitivity analysis identifies the xCT antiporter as a common triple-negative breast tumor therapeutic target. Cancer Cell 2013 Oct 3 [Epub ahead of print].

Apoptosis

Major finding: BAK is preferentially activated by BID, whereas BAX is preferentially activated by BIM.

Clinical relevance: *BAK1* loss is associated with poor response to drugs that induce BID-dependent apoptosis.

Impact: Nonredundant roles of BID and BIM may have implications for the effectiveness of cancer therapy.

PROAPOPTOTIC BH3-ONLY PROTEINS HAVE DIFFERENT ACTIVATION PREFERENCES

Many chemotherapeutic agents activate the mitochondrial apoptotic pathway, which is regulated by proapoptotic BCL-2 protein family members such as BID and BIM. BID and BIM activate BAK and BAX, which then oligomerize and commit the cell to death by directly inducing mitochondrial outer membrane permeabilization (MOMP). Although BID and BIM have differential expression patterns and can be induced by distinct apoptotic stimuli, it has been assumed that BID and BIM are functionally redundant activators of BAK and BAX. Using a fluorescence-based assay to detect mitochondrial transmembrane potential, Sarosiek and colleagues showed that the mitochondrial response to a BID peptide was attenuated in *Bak*$^{-/-}$, but not *Bax*$^{-/-}$ murine embryonic fibroblasts (MEF), whereas the response to a BIM peptide was reduced only in *Bax*$^{-/-}$ MEFs. Moreover, in MEFs lacking BID and BIM, a lower concentration of exogenous BID than BIM was needed to induce BAK oligomerization, whereas the opposite was true for BAX oligomerization. These findings suggest that, although BID and BIM are each capable of activating BAK and BAX, BID preferentially activates BAK and BIM preferentially activates BAX, a trend which was observed in multiple cell types. Intriguingly, *Bak*$^{-/-}$ MEFs were also less sensitive to drugs such as topoisomerase inhibitors that induce MOMP in a BID-dependent manner, raising the possibility that BAK deficiency in tumors may confer resistance to these agents. An analysis of patients with high-grade serous ovarian adenocarcinomas revealed that 23.2% of patients treated with topoisomerase inhibitors had heterozygous or homozygous loss of *BAK1*, and that loss of one or both alleles was significantly associated with shorter overall survival. Although the mechanisms underlying BAK and BAX activation preferences remain to be identified, these results suggest that the BAK and BID status of patients should be considered prior to treatment with certain chemotherapeutic agents. ■

Sarosiek KA, Chi X, Bachman JA, Sims JJ, Montero J, Pavel L, et al. BID preferentially activates BAK while BIM preferentially activates BAX, affecting chemotherapy response. Mol Cell 2013;51:751–65.

Note: *Research Watch* is written by *Cancer Discovery* Science Writers. Readers are encouraged to consult the original articles for full details. For more Research Watch, visit *Cancer Discovery* online at http://CDnews.aacrjournals.org.