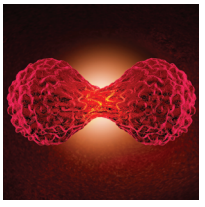
Mitosis

Major finding: MYC promotes the apoptotic response to antimitotic drugs by regulating BCL-XL and BH3-only proteins.

Approach: An unbiased screen identified genes that induce death in mitosis in response to taxol.

Impact: MYC and BCL-XL represent potential therapeutic targets and biomarkers of taxane efficacy.

MYC SENSITIZES CANCER CELLS TO ANTIMITOTIC THERAPIES



Mitotic arrest can result in cell death in mitosis (DiM) or slippage, in which a cell survives, returning to interphase without cell division. Taxol and other antimitotic drugs are effective treatments for several cancers, but the molecular mechanisms underlying the induction of apoptosis during mitotic arrest have not been established. Topham and colleagues performed a genome-wide siRNA screen to identify candidate regulators of DiM. Among the candidate genes, depletion of MYC or its target early growth response 1 inhibited DiM and shifted cell fate in favor of slippage, suggesting that MYC sensitizes cells to apoptosis during mitotic arrest. In support of this idea, MYC inhibition resulted in reduced apoptotic responses to various antimitotic cancer therapies in nine of 12 cancer cell lines. In addition, MYC promoted postmitotic apoptosis following slippage in a p53-independent manner. Mechanistically, MYC regulated DiM by downregulating expression of the gene encoding BCL-XL, an antiapoptotic factor, and by upregulating expression of genes encoding three proapoptotic BH3-only proteins, BID, BIM, and NOXA, which functioned as redundant downstream effectors of MYC. Depletion of MYC enhanced cell survival in response to low-dose taxol, whereas inhibition of BCL-XL restored apoptosis in the absence of MYC. Conversely, MYC overexpression accelerated DiM and augmented postmitotic cell death; consistent with this finding, elevated MYC levels were correlated with improved responses to antimitotic drugs in cancer cell lines and patients. These results identify MYC as a determinant of cell fate during mitotic arrest and a potential biomarker of taxane efficacy, and suggest that inhibition of BCL-XL may be effective in combination with antimitotic agents. ■

Topham C, Tighe A, Ly P, Bennett A, Sloss O, Nelson L, et al. MYC is a major determinant of mitotic cell fate. Cancer Cell 2015;28:129–40.

Breast Cancer

Major finding: Progesterone receptor (PR) modulates ERα transcriptional activity to inhibit breast cancer growth.

Mechanism: PR redistributes ERα binding to antiproliferative genes in the presence of estrogen and progesterone.

Impact: Copy-number loss of the gene encoding PR is common in ERα$^+$ breast cancer and associated with poor outcome.

PROGESTERONE RECEPTOR DETERMINES ERα FUNCTION

Expression of the progesterone receptor (PR, encoded by the *PGR* gene) is associated with response to endocrine therapy, decreased metastasis, and improved prognosis in patients with estrogen receptor α–positive (ERα$^+$) breast cancer. Although PR is frequently used as a marker of active ERα signaling and both receptors have been shown to interact, whether there is functional cross-talk between PR and ERα is unknown. Mohammed and colleagues found that, in the presence of estrogen, progesterone stimulation triggered recruitment of PR to chromatin and interaction of PR with ERα and its cofactors in ERα$^+$PR$^+$ breast cancer cell lines. This progesterone-induced interaction resulted in a rapid and global redistribution of ERα chromatin binding to a distinct set of genes marked by binding of the coactivator p300 and harboring progesterone-responsive elements, suggesting that PR mediates this change in ERα binding and modifies ERα transcriptional activity. Indeed, ERα reprogramming in response to dual treatment with estrogen and progesterone resulted in an altered gene expression profile enriched in genes associated with cell death, apoptosis, and differentiation. Consistent with this finding, progesterone treatment decreased estrogen-induced proliferation and inhibited estrogen-driven ERα$^+$ tumor growth in xenograft models and primary human ERα$^+$PR$^+$ breast tumor explants. Furthermore, dual treatment with the ERα antagonist tamoxifen and progesterone more effectively suppressed estrogen-stimulated tumor growth. Copy-number loss of the *PGR* locus was found to be a common event in ERα$^+$ breast cancer, with heterozygous or homozygous *PGR* deletion occurring in 21% of patients, and was associated with poor clinical outcome in one third of patients with luminal B tumors and in a subset of patients with luminal A tumors. These results demonstrate a functional interplay between the ERα and PR steroid receptors and suggest that PR modulates ERα transcriptional activity under estrogenic conditions to block ERα$^+$ breast cancer proliferation and tumorigenicity. ■

Mohammed H, Russell IA, Stark R, Rueda OM, Hickey TE, Tarulli GA, et al. Progesterone receptor modulates ERα action in breast cancer. Nature 2015;523:313–7.

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