THERAPEUTICS

It works, but how?

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Histone deacetylase inhibitors (HDACIs) lead to global histone hyperacetylation, apoptosis and anticancer effects, but the targets of these inhibitors are not well understood. René Bernards and colleagues used functional genetic screening to find out which pathways could confer cellular resistance to HDACI. Derepression of retinoic acid (RA) signalling is one mechanism by which HDACIs exert their cytotoxic effects.

The HDACI PXD101 was used to screen a human complementary DNA (cDNA) expression library in p53-deficient mouse embryo fibroblasts (MEFs) with an oncogenic Ras^{v12} gene. The small numbers of infected cells that formed colonies despite exposure to PXD101 were picked and the proviral inserts were sequenced. cDNAs for the nuclear hormone receptor transcription factor RA receptor α (RARα) and the tumour antigen preferentially expressed antigen of melanoma (PRAME), which is a repressor of RA signalling, were identified in these colonies. When these cDNAs were cloned and introduced into Ras^{v12} MEFs they conferred resistance to PXD101 and other HDACIs of different chemical classes, although histones were still acetylated. The HDACIs were found to induce RARα transactivation, suggesting that derepression of the RA pathway is one mechanism through which HDACIs exert their anticancer activity.

The authors next asked what effect treatment with both RA and PXD101 would have on cancer cells. Mice with xenografted A375 melanoma cells and A375 cells expressing an RNA interference *PRAME* construct (A375–$PRAME^{KD}$) were given RA, PXD101 or both, daily. A375 tumours were fully resistant to both agents alone and combined. However, A375–$PRAME^{KD}$ tumours were growth-inhibited when tumours were treated with RA and PXD101 together.

These experiments show that the RA pathway is a rate-limiting target of HDACIs and that by increasing RA signalling the therapeutic efficacy of HDACIs might be enhanced.

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ORIGINAL RESEARCH PAPER Epping, M. T. *et al.* A functional genetic screen identifies retinoic acid signaling as a target of histone deacetylase inhibitors. *Proc. Natl Acad. Sci. USA* **104**, 17777–17782 (2007)

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