## NIR is a novel INHAT repressor that modulates the transcriptional activity of p53

Most transcriptional repression pathways depend on the targeted deacetylation of histone tails. We characterize NIR, a novel transcriptional corepressor with inhibitor of histone acetyltransferase (INHAT) activity. NIR (Novel INHAT Repressor) is ubiquitously expressed throughout embryonic development and adulthood. NIR is a potent transcriptional corepressor that is not blocked by histone deacetylase inhibitors and is capable of silencing both basal and activator-driven transcription. NIR directly binds to nucleosomes and core histones and prevents acetylation by histone acetyltransferases, thus acting as a bona fide INHAT. Using a tandem affinity purification approach, we identified the tumor suppressor p53 as a NIR-interacting partner. Association of p53 and NIR was verified in vitro and in vivo. Upon recruitment by p53, NIR represses transcription of both p53-dependent reporters and endogenous target genes. Knock-down of NIR by RNA interference significantly enhances histone acetylation at p53-regulated promoters. Moreover, p53-dependent apoptosis is robustly increased upon depletion of NIR. In summary, our findings describe NIR as a novel INHAT that plays an important role in the control of p53 function.

## Gene regulation by histone demethylation

Gene regulation in eukaryotes requires the coordinate interaction of chromatin-modulating proteins with specific transcription factors such as the androgen receptor. Gene activation and repression is specifically regulated by histone methylation status at distinct lysine residues. Lysine-specific demethylase 1 (LSD1; also known as BHC110) co-localizes with the androgen receptor in normal human prostate and prostate tumour. LSD1 interacts with androgen receptor in vitro and in vivo, and stimulates androgen-receptor-dependent transcription. Conversely, knockdown of LSD1 protein levels abrogates androgen-induced transcriptional activation and cell proliferation. Chromatin immunoprecipitation analyses demonstrate that androgen receptor and LSD1 form chromatin-associated complexes in a ligand-dependent manner. LSD1 relieves repressive histone marks by demethylation of histone H3 at lysine 9 (H3-K9), thereby leading to de-repression of androgen receptor target genes. Furthermore, we identify pargyline as an inhibitor of LSD1. Pargyline blocks demethylation of H3-K9 by LSD1 and consequently androgen-receptor-dependent transcription. Thus, modulation of LSD1 activity offers a new strategy to regulate androgen receptor functions. Here, we link demethylation of a repressive histone mark with androgen-receptor-dependent gene activation, thus providing a mechanism by which demethylases control specific gene expression.