doi:10.1038/nature19469

CANCER

# Acidic shield puts a chink in p53's armour

**Underactivity of the transcription factor p53 can lead to tumour development. The discovery that the SET protein binds to and inhibits p53 points to a way to unleash the tumour suppressor's activity.**

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In human history, possession of unbridled power has typically ended badly. The same is true in biology, as illustrated by studies of the tumour-suppressor protein p53. Stringent control is required to restrain this transcription factor's potent ability to cause cell death, arrest a cell in stasis or alter the course of metabolism. However, these controls need to be reversible, because p53 must be rapidly activated to protect cells from a wide variety of cellular stresses that promote tumour development[1]. In a paper online in *Nature*, Wang *et al.*[2] reveal a previously unknown mechanism of restraining p53, which involves the formation of a reversible, acidic protein 'shield' that prevents the carboxy-terminal end of p53 from interacting with the cell's transcriptional machinery.

The carboxy-terminal domain (CTD) of p53 is a veritable hub of regulatory signalling. The six lysine residues within this 30-amino-acid region can be modified by several different types of molecule to alter how p53 regulates target genes, the stability of the protein, or its interactions with target DNA[1]. For instance, the addition of acetyl molecules to these lysine residues in response to cellular stressors such as DNA damage activates p53, leading to the transcription of target genes. But despite much research, exactly how this lysine acetylation controls p53's activity has remained unclear.

To drill down into this question, Wang and colleagues began with an unbiased, biochemical approach to identify proteins that interact with the p53 CTD, both when the protein is activated by lysine acetylation and when it lacks acetyl groups and is inactive. Surprisingly, and in contrast to previous studies, the authors found no proteins that bound to the acetylated CTD under their assay conditions, and only one, the tumour-promoting SET protein, that interacted with the unacetylated CTD.

The researchers show that SET acts as a transcriptional co-repressor, inhibiting p53's transcription-factor activity when bound to the CTD (Fig. 1). This inhibition relies on reversible electrostatic interactions between

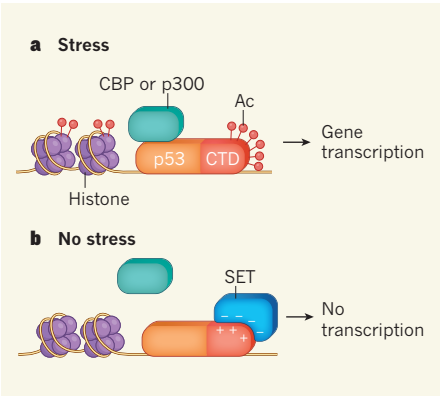


**Figure 1 | A shield model of p53 regulation.** **a**, Under conditions of cellular stress, acetyl groups (Ac) are added to six lysine amino-acid residues in the carboxy-terminal domain (CTD) of the tumour-suppressor protein p53. The protein binds to target DNA sequences and interacts with one of the two co-activator proteins CBP and p300, which acetylate DNA-associated histone proteins. These interactions together promote gene transcription. **b**, Wang *et al.*[2] report that, in the absence of stress and lysine acetylation, a highly acidic, negatively charged domain of the protein SET binds to the positively charged p53 CTD. Although SET-bound p53 can bind DNA, it cannot interact with p300 or CBP, and thus transcription is inhibited.

positively charged, basic amino acids in the unacetylated p53 CTD and a region of SET comprising long stretches of clustered, highly acidic and negatively charged amino acids. SET–CTD binding does not disrupt p53's interaction with its target DNA-binding sites, meaning that inactive p53 is poised to activate target genes, which is probably beneficial for a rapid stress response. Instead, SET acts as a shield, preventing the transcriptional co-activator proteins p300 and CBP from interacting with p53 and with nearby DNA and associated histone proteins, and so blocking target-gene activation in the absence of cellular stress.

Wang *et al.* defined highly acidic domains, such as that described for SET, as stretches of at least 46 amino acids, of which more than 76% of residues are acidic and are found in clusters across the domain. The authors searched the UniProt database[3] for other highly acidic domain proteins, and found only 49 that fitted these criteria, including the p53-interacting proteins DAXX, PELP1 and VPRBP. The group demonstrated that these proteins can bind to the unacetylated, but not the acetylated, p53 CTD. This finding suggests a broad regulatory role for highly acidic domain proteins in an acetylation switch network, which probably extends beyond p53. However, it is puzzling that these proteins were not identified in Wang and colleagues' original screen. Moreover, it is difficult to reconcile the researchers' shield model of acidic-protein-mediated p53 inhibition with previous characterizations of DAXX (ref. 4) and PELP1 (ref. 5) as stress-dependent co-activators of p53.

The physiological importance of interactions between regulatory proteins and the p53 CTD has been established by engineering mice lacking this domain, which die within two weeks of birth[6,7]. Wang *et al.* mutated the six lysine residues in the p53 CTD to glutamines, which mimic the charge and structure of acetylated lysine and so effectively model permanent lysine acetylation. As such, mice harbouring this mutation lack SET binding to the CTD. These animals died within one day of birth, owing to unchecked cell death in the brain and severe neurological defects, underscoring the need for tight control of p53 activity during embryonic development.

By contrast, it has been shown[8] that replacement of lysine with arginine, which mimics a total lack of lysine acetylation — and, presumably, constitutive SET binding — produces no developmental anomalies. To confirm that these effects are attributable to SET, rather than to other highly acidic domain proteins, the authors deleted the mouse gene that encodes SET, which caused embryonic defects and death just before or after birth. Further studies are needed to determine whether this lethality results solely from unchecked p53 activation, or whether other functions of SET are also involved.

SET is a known tumour-promoting protein, and is aberrantly expressed in various cancers of the blood[9] and in solid tumours[10]. Previous studies of SET (for example, ref. 10) have focused mainly on its role as an inhibitor of protein phosphatase 2A (PP2A) — a tumour-suppressor protein that represses multiple signalling pathways that are aberrantly activated in many cancers, including the c-Myc, Wnt and PI3K/Akt pathways. Thus, therapies that inhibit SET may offer opportunities to treat cancer beyond simply unleashing p53. But such treatments must also take into consideration the complex consequences of altering SET activity.

In support of the therapeutic potential of

targeting SET, Wang *et al.* showed that inhibition of SET production in mice led to regression of tumours with normal p53 levels, but not of tumours lacking the protein. However, concerns remain. For instance, tumours frequently harbour single-nucleotide mutations that alter the amino-acid sequence of p53 and so lead to production of a mutant protein. Disrupting SET–p53 interactions in cells carrying such mutations might lead to activation of a mutant protein that has deleterious tumour-promoting activities.

Profiling of the genomic regions with which SET is associated is now needed to determine: the breadth of p53-regulated genes affected by SET; whether SET's role is restricted to specific developmental stages or tissues; and whether p53 mutations that are implicated in cancers alter SET control and response. Moreover, studies that used SET inhibitors to increase PP2A activity in cancer[10] should be reinterpreted in light of the newly revealed role of SET as a protein shield. Combining SET inhibitors with drugs that inhibit lysine deacetylation[11] may offer effective therapeutic strategies in cancer treatment. ■

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