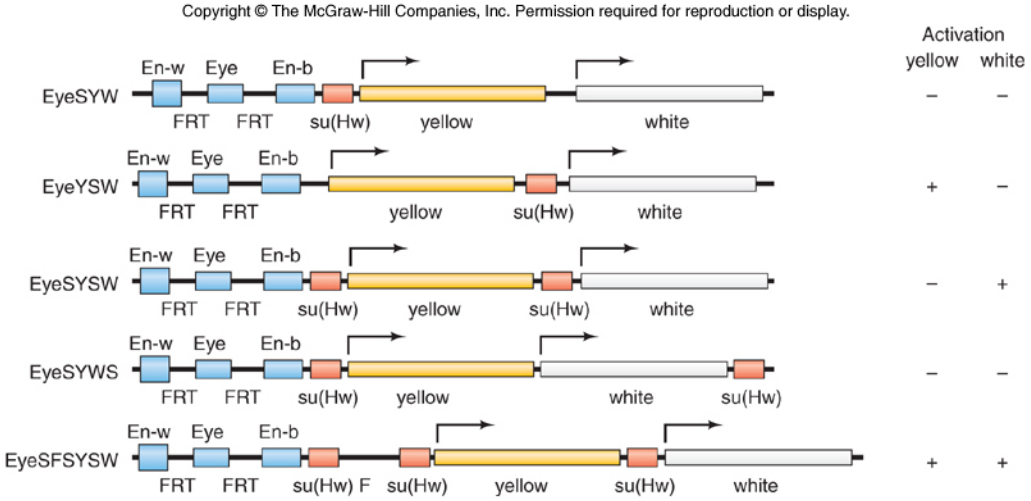
Combinatorial code

- Different combinations of transcription activators (and/or other cofactors) produce different evels of expression of a given gene or set of genes in different cellular, development, or environmental conditions.
- Combinatorial controls ensure a gene or set of genes are tunred on at the right time and right place to perform specific functions, or specify certain cell/tissue/organ types.
- Formation of enhanceosome is one way to implement combinatorial control.

Insulators

- DNA elements that can shield genes from activation or repression
- two functional hypotheses: sliding model (block enhancers/silencers), looping model (dimers form loops to isolate enhancers/silencers from promoter)
- two or more insulators can cancel or enhance each other's effects



Regulation of transcription factors

Signal transduction pathways can modify transrciption factors, regulating their activity.

- phosphorylation
- ubiquitination
- acetylation
- methylation
- others

Example: p53 tumor suppressor protein

- atypical binding domain
- promotes growth arrest, apoptosis, and cell senescence
- regulates many genes
- regulated by many genes

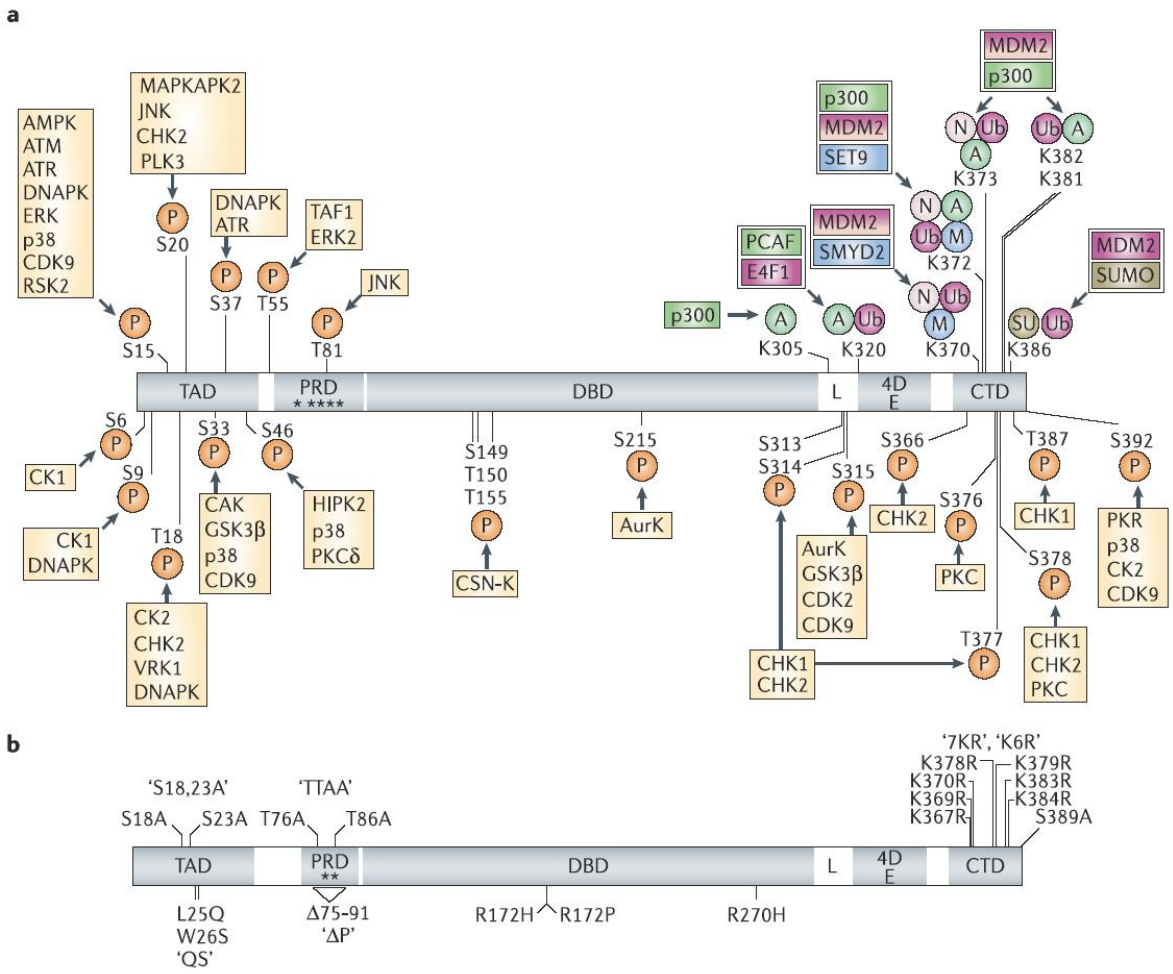


Figure 2 | **Comparative maps from *in vitro* human p53 and *in vivo* mouse p53 studies. a** | Post-translational

Acetylation

- acetylation of p53 (in C terminal domain) enhances DNA binding activity
- p53 is fully acetylated on DNA damage and correlates with expression of p53 target genes (p21 particularly)

Phosphorylation

- HIPK2 is activated by UV radiation and phosphorylates p53
- p53 acetylation (by CBP/p300) is dependent on phosphorylation by HIPK2
- enhances expression of p53 gene targets (esp. p21)
- HIPK2 inhibits cell proliferation, results in growth arrest and apoptosis

Ubiquitination

- MDM2 does not affect p53 mRNA
- MDM2 causes a reduction of p53
- MDM2 ubiquitinates p53

- USP10 stabilizes and deubiquitinates p53, promotes p53 activity
- MDM2 moves p53 to cytoplasm by ubiquitination
- USP10 deubiquitinates p53
- under unstressed conditions, MDM2 succeeds and p53 is degraded; under genotoxic stress conditions, USP10 succeeds and p53 gene targets are expressed, apoptosis elicited

Methylation

- Set9 has specificay methyltransferase activity, specific to p53 and H3
- p53 is not methylated by many common methyltransferases
- Set9 methylates p53 at K372
- Set9 enhances expression of p53 target genes
- Smyd2 methylates p53 at K370
- Smyd2 represses p53 function
- crosstalk between Set9 and Smyd9; methylation of K370 has no affect on methylation of K372, but methylation of K372 shuts down methylation of K370