The p53 family in cancer biology

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The p53 family members p73 and p63 are involved in female infertility maternal reproduction (Nature Rev MCB 2011;12,4:259) and as well as in cancer formation (TiBS 2 014;39,4:191). We identified their activation during DNA damage, several transcriptional targets, the mechanisms of regulation of cell death, and the protein degradation pathway.To understand the p53 structure-function relationship, we perform ed a molecular dynamics study, showing an induced-fit interaction of the C-terminal domain with the DNA-binding domain. Direct intra- and intermonomeric long-range communications between the tetramerization and DNA-binding domains are noted, providing a biophysical rationale for the reported functional regulation of the p53 C-terminal region. We also detect 'dynamic' deformations switched on and off by particular p53 tetrameric conformations and measured by the roll and twist parameters in the same base pairs. These different conformations can indeed modulate the electrostatic potential isosurfaces of the whole p53-DNA complex (Oncogene, in press PMID: 26477317).While TAp73-/- mice show high tumor incidence with hippocampal dys egensis, they show an elevated cancer incidence. Accordingly, TAp73 opposes HIF-1 activity, affecting tumour angiogenesis. TAp73 interacts with HIF-1a, promoting HIF-1a po lyubiquitination and consequent proteasomal degradation. These findings demonstrate a novel mechanism for HIF-1 regulation and provide an additional explanation for the

molecular basis of the growth, progression, and invasiveness of human cancers. (PNAS-USA 2015;112,1:226) (TiBS 2015;40,8:425). P63 is a determinant of skin development. Using a MMTV-ErbB2 murine model, we found that ΔNp63 regulates mammary Cancer Stem Cells self-renewal and breast tumorigenesis via the direct transactivation of Sonic Hedgehog (Shh), GLI family zinc finger 2 (Gli2), and Patched1 (Ptch1) genes. (PNAS-USA 2015. 112,11: 3499-504. PMID: 25739959). At least in part, this seems to be exerted by regulation of the metabolism via Hexokinase II (PNAS-USA 2015. 112,37: 11577-82. PMID: 26324887).