Cytochrome c regulates SET-mediated acetylation of the C-terminal domain of p53

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The C-terminal domain (CTD) of p53 is a target for acetylation; which can be negatively regulated by the oncoprotein SET1. The acidic-domain-containing SET binds the CTD of p53 primarily through electrostatic interactions. However, during cell stress CTD-acetylation displaces SET by masking CTD lysine residues. What's more, this mechanism of acetylation-mediated regulation corresponds to a conserved mode of post-translational protein interaction control. In a recent study, we showed that the haemprotein Cytochrome c (Cc) interacts with SET (KD ca. 3.1 ⌣M) during DNA damage2. Thus, Cc may modulate the SET/p53-CTD interaction under stress conditions.
Nuclear magnetic resonance (NMR) and isothermal titration calorimetry (ITC) experiments were performed to determine the nature of such interaction. ITC studies confirmed un-acetylated (KD ca. 3 ⌣M) but not acetylated p53-CTD binds SET. Next, 1D 1H NMR - tracking Cc Met80-εCH3 – was used to assess the competition between p53-CTD and Cc for SET. Increasing concentrations of p53-CTD led to dissociation of Cc from SET and recovery of the Met80-εCH3 signal, indicating p53-CTD is able to compete with Cc for SET binding.
1D 19F NMR was then used to monitor a 19F-Phe-CTD p53 peptide. Increasing concentrations of Cc caused the signal corresponding to 19F-Phe-CTD to be partially recovered (but not fully due to conformational exchange in the peptide). These data suggested competition between p53-CTD and Cc for SET binding. Further studies will seek to better characterise p53-CTD dynamics in relation to SET binding as well as corroborating biophysical data obtained with whole-cell assays.

1. Wang, D et al. (2016). Acetylation-regulated interaction between p53 and SET reveals a widespread regulatory mode. Nature 1038(10): 118-121
2. González-Arzola, K et al. (2015). Structural basis for inhibition of the histone chaperone activity of SET/TAF-Iβ by cytochrome c. PNAS 112(32): 9908-9913