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The relationship between the structural properties of p53 binding sites and p53-dependent gene expression

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The tumor suppressor protein is a central hub protein in human cells. In response to stress, it functions mainly as a transcription factor (TF), binding to more than 200 response elements (REs), activating and repressing adjacent genes. The REs are made of two sequence-specific half-sites, separated by a variable number of base pairs. It is currently unclear how p53 chooses its target sites, however, p53 multi-functional activities are directly linked to its ability to function as a sequence-specific TF. It is now well appreciated that the intrinsic physical properties of the DNA double helix can affect binding of TFs and transactivation of adjacent genes. We have previously shown that DNA structure and flexibility vary among p53 REs, affecting their binding characteristics. We carried out experimental measurements of global structure and flexibility properties of p53 REs using cyclization kinetics of DNA minicircles, together with binding studies and transactivation assays in yeast and human cells. We propose that functional selectivity is conferred at least in part through p53/DNA binding and that differential structural characteristic of p53 REs play a role in this selectivity. I will present recent experimental results showing how p53 uses the structural properties of its binding sites to differentiate between functional classes of p53 REs, that p53 REs are allosteric effectors of p53 transactivation and the novel role of the spacer sequences in these interactions. These recent findings reveal how non-canonical sites, such as half-sites can be functional and hence expand the "universe" of p53 binding sites.

Biography

Tali E Haran is an Associate Professor at the Department of Biology, Technion-Israel Institute of Technology. She holds PhD and Master Degree from the Weizmann Institute of Science, studying the crystal structure of DNA oligomers. She has completed her Postdoctoral studies at Yale University, studied DNA bending and indirect recognition in protein-DNA interactions. She has been a Visiting Scientist at the Department of Biochemistry, Cambridge University, UK at the Department of Biochemistry and Molecular Biology, Columbia University, USA and at the Centre for Integrative Biology, University of Trento, Italy. Her main research interest is the interactions between sequence-specific transcription factors and their DNA binding sites, focusing on the mechanism by which DNA structure contributes to the recognition of particular sites by regulatory proteins.

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