# DIR RESEARCH UPDATE

## THE EXPANDING UNIVERSE OF p53 TARGETS

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Among the most prominently studied regulators of gene function in humans is the p53 tumor suppressor. Mutant or dysregulated p53 is associated with nearly all cancers, demonstrating the central role that it plays in maintaining healthy tissue. Discovered over 30 years ago, initially as a factor that could associate with a viral oncogene, p53 is critical for cell cycle regulation and apoptosis following cellular stress. In recent years, the role of p53 in human biology has been extended to DNA repair, angiogenesis, cellular metabolism, autophagy, prevention of viral propagation, stem cell renewal, fertility, meiotic recombination, differentiation, cellular reprogramming, and now innate immunity. Just how this protein can factor into so many activities in the body continues to be the subject of a vast literature.

While p53 can have many roles within the cell, the tumor suppressive function is primarily associated with its ability to act as a transcriptional master regulator. p53 directly targets transcriptional control of a large number of genes (over 200) and noncoding sequences in the human genome, many of which can coordinate cellular life and death responses to a variety of internal and external stresses.

Knowledge of p53 binding to target response element (RE) sequences and the potential of p53 to drive transcription is essential to understanding how p53 acts as the so-called “guardian of the genome.” The canonical consensus target for p53 was generally accepted to consist of two decamer half-sites (RRRCWWGYYY) separated by a variable spacer. We have sought to define the p53 network in terms of *functionality* of REs, that is, the ability of REs to support transactivation by wild-type and several cancer-associated mutant p53 proteins. Using a variety of yeast-based and human tissue culture approaches, we have identified a greatly expanded universe of potential functional p53 targets that has led to a greater appreciation of the complex roles for p53 in cancer and human biology. These findings are presently being expanded to ChIP-Seq analyses of p53-DNA interactions in human primary and cancer cells.

Armed with rules for RE functionality we have been investigating the evolution of p53 networks, identifying single-nucleotide polymorphisms (SNP) affecting inclusion of genes into the functional network, characterizing p53 target sequences that are not canonical, and addressing interactions between the estrogen receptor and the p53 networks. [Some of the relevant papers are listed on the next page.] Over the past year, through a collaboration with the recently created Clinical Research Unit, we identified an important role for p53 in the Toll-like receptor (TLR) component of the human innate immunity pathway using primary lymphocytes and alveolar macrophages from healthy subjects. Included in these findings is a SNP in a TLR8 promoter sequence that alters p53 responsiveness.

We anticipate that this body of information, including observations of considerable differences between individual human subjects, will provide new translational opportunities related to p53 function and individual responses to environmental challenges.

The activities of the Chromosome Stability Group focus on a) mechanisms of genome change and protection from environmental chromosomal damage in yeast and human cells and b) the human p53 master regulatory network and mechanisms of p53 function. The following is a sampling of p53-related papers from the Group.


Resnick MA, Inga A. Functional mutations in the sequence-specific transcription factor p53 and implications for master genes of diversity. *Proc. Natl. Acad. Sci. U.S.A.,* 100: 9934-9939, 2003.

Tomso DJ, Inga A, Menendez D, Pittman GS, Campbell MR, Storici F, Bell DA, Resnick MA. Identification of functionally distinct polymorphic sequences that are targets for p53 transactivation. *Proc. Natl. Acad. Sci. U.S.A.,* 102: 6431-6436, 2005.

Menendez D, Inga A, Resnick MA.The biological impact of the human master regulator p53 can be altered by mutations that change the spectrum and expression of its target genes. *Mol. Cell. Biol.,* 26: 2297-2308, 2006.

Menendez D, Krysiak O, Inga A, Krysiak B, Resnick MA*, Schönfelder G*. A SNP in the FLT1 promoter integrates the VEGF system into the p53 transcriptional network. *Equal contributions. *Proc. Natl. Acad. Sci. U.S.A.,* 103: 1406-1411, 2006.

Jegga AG, Inga A, Menendez D, Aronow BJ, Resnick MA.Functional evolution of the p53 regulatory network through its target response elements. *Proc. Natl. Acad. Sci. U.S.A.,* 105: 944-949, 2008.

Jordan JJ, Menendez D, Inga A, Noureddine M, Bell DA, Resnick MA. Noncanonical DNA Motifs as transactivation targets by wild type and mutant p53. *PLoS Genet.,* 4: e1000104, 2008.

Menendez D, Inga A, Resnick MA. The expanding universe of p53 targets. *Nat. Rev. Cancer,* 9: 724-737, 2009.

Menendez D, Inga A, Resnick MA. Estrogen receptor acting *in cis* enhances WT and mutant p53 transactivation at canonical and noncanonical p53 target sequences. *Proc. Natl. Acad. Sci. U.S.A.,* 107: 1500-1505, 2010.

Menendez D, Shatz M, Garantziotis S, Fessler M, Resnick MA. The human Toll-like receptor family is integrated into the DNA damage and p53 response network. Submitted.