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p53

UNDERSTANDING THE ACTIONS OF 53BP1

The role of p53-binding protein 1 (53BP1) — a p53-interacting protein — in DNA repair is well defined, although it is less clear how it influences p53 biology. Now, Cuella-Martin *et al.* reveal that 53BP1 modulates p53-mediated transcription and that this function of 53BP1 is independent of its role in DNA repair.

The authors found that the transcriptional changes induced by Nutlin-3 (a small molecule) or ionizing radiation (both of which activate p53 transcription to induce growth arrest) in cells expressing wild-type p53 were reduced in both *TP53*- and *53BP1*-knockout cells, suggesting that 53BP1 promotes p53-mediated transcription.

As the carboxy-terminal tandem BRCT domain of 53BP1 was found to mediate 53BP1–p53 interactions, the authors generated cell lines in which this domain was deleted. These cells showed a decrease in the p53-mediated transcriptional response, but not in 53BP1-dependent DNA repair. Thus, the roles of 53BP1 in these processes are independent, and its involvement in the p53 response is regulated by its BRCT domain.

The authors also revealed that the ubiquitin-specific protease USP28 interacts with the BRCT domain of 53BP1 at a distinct site to p53, suggesting that 53BP1 and USP28 can bind to p53 at the same time. Furthermore, as knockout of *USP28* caused resistance to Nutlin-3-induced growth arrest that was not enhanced by co-depletion of *53BP1*, and 53BP1 and USP28 both promoted the binding of p53 to p53-responsive elements, 53BP1 and USP28 seem to cooperate to regulate p53-mediated transcription.

In short, 53BP1 interacts with p53 and USP28 to modulate p53-mediated transcription; this role is independent of the functions of 53BP1 in DNA repair.

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ORIGINAL ARTICLE Cuella-Martin, R. *et al.* 53BP1 integrates DNA repair and p53-dependent cell fate decisions via distinct mechanisms. *Mol. Cell* http://dx.doi.org/10.1016/j.molcel.2016.08.002 (2016)