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URLs
P53
http://ca.expasy.org/uniprot/P02340

ATM
http://ca.expasy.org/uniprot/Q62388

MRE11
http://ca.expasy.org/uniprot/Q61216

NBS1
http://ca.expasy.org/uniprot/Q9R207

P53

Heads or tails? You lose!

> “…the mechanism that underlies such gain-of-function p53 mutants.”

Mutations in the tumour suppressor p53 generally cause the loss of tumour-suppressor function. However, some p53 mutants have novel activities that promote oncogenesis. A new study in *Nature Cell Biology* sheds light on the mechanism that underlies such gain-of-function p53 mutants.

Song *et al*. introduced the most common p53 missense mutations, R248W and R273H, independently into the humanized p53-knock-in allele (p53hki) in mice. The p53hki protein is functionally equivalent to endogenous mouse p53, but consists primarily of the human p53 sequence. Therefore, the effect of a cancer mutation on human p53 is recapitulated more faithfully.

R248W mice developed a diverse spectrum of sarcomas and lymphomas that was more complex than that observed in *Trp53*$^{-/-}$ mice, and whereas mutant p53 was undetectable in pretumour thymocytes, it accumulated in thymoma cells derived from R248W mice. Whereas interchromosomal translocations are rarely found in *Trp53*$^{-/-}$ cells, they were present in 78% of pretumour R248W thymocytes. What causes this type of genetic instability? The answer might lie in the authors’ finding that the G2–M checkpoint was impaired in R248W and R273H cells following ionizing radiation, whereas the checkpoint was normal in irradiated *Trp53*$^{-/-}$ cells.

Following DNA damage, activated ataxia telangiectasia mutated (ATM) kinase is recruited to the site of DNA damage and triggers the G2–M checkpoint by phosphorylating histone variant H2AX and other substrates at the site of DNA damage. Song *et al*. showed that the recruitment of activated ATM was disrupted and that ATM-dependent phosphorylation of H2AX and other substrates was impaired in R248W and R273H cells.

The MRN (MRE11–RAD50–NBS1) complex is important for sensing DNA double-strand break (DSB) damage and for recruiting ATM. Using a double-stranded-DNA pull-down assay, the authors recovered DSB-bound proteins; the association of MRE11, NBS1 and ATM with DSBs was reduced in R248W and R273H mutant cells compared with *Trp53*$^{-/-}$ cells. Co-immunoprecipitation experiments revealed the physical interaction between R248W or R273H and MRE11, whereas wild-type p53 did not interact with MRE11 after low dosages of ionizing radiation. Together, these data suggest that the physical interaction between p53 mutants and MRE11 disrupts the recruitment of the MRN complex to the site of DNA damage, leading to ATM inactivation, checkpoints defects and genetic instability.

The authors argue that “a novel gain-of-function of common p53 cancer mutants in disrupting critical DNA DSB damage responses will have significant implications on the therapeutic interventions for human cancers that express p53 cancer mutants.”

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ORIGINAL RESEARCH PAPER Song, H. *et al.* p53 gain-of-function cancer mutants induce genetic instability by inactivating ATM. *Nature Cell Biol.* 8 Apr 2007 (doi:10.1038/ncb1571)