TUMOUR SUPPRESSION

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Evidence indicates that MDM2 and MDM4 (also known as MDMX) have non-redundant roles in regulating p53 stability in response to numerous stress signals, including the DNA damage response to double strand breaks (DSBs) and oncogene hyperactivation. Geoffrey Wahl and colleagues now provide insight into the part played by MDM4 in regulating the activity and therefore the tumour-suppressive effects of p53.

To examine the importance of MDM4 in regulating p53 stability in response to DSBs Wang and colleagues generated an MDM4-mutant mouse in which three key serine residues that are phosphorylated by the DNA damage response kinases ataxia-telangiectasia mutated (ATM; Ser402) and CHK2 (Ser341 and Ser367) were mutated to alanine (*Mdm4*^{3SA} mice). These mice were not tumour-prone and did not exhibit any defects in development. Using mouse embryonic fibroblasts (MEFs) derived from embryonic day 13 *Mdm4*^{3SA} embryos the authors found that MDM4-3SA was resistant to DSB-induced degradation, which correlated with reduced p53 levels. Next, they assessed whether p53 activity was impaired in response to DSBs in MDM4-3SA MEFs and thymocytes by analysing the induction of the p53 target genes *Cdkn1a* (which encodes the checkpoint protein p21) and *Puma* (which encodes a pro-apoptotic protein and is also known as *Bbc3*). They found that total mRNA levels of *Cdkn1a* and *Puma* were significantly reduced. The MEFs exhibited impaired (but not absent) DNA damage-induced cell cycle checkpoint arrest, and the thymocytes exhibited reduced DNA damage-induced apoptosis. Furthermore, *Mdm4*^{3SA} mice were largely resistant to whole-body (10 Gy) irradiation, which causes lethality in wild-type mice.

Heterozygous loss of *Mdm4* has previously been shown to delay *Myc*-induced lymphomagenesis, indicating that MDM4 is also important in regulating p53 activation in response to oncogene-induced stress. Therefore, Wang and colleagues crossed *Mdm4*^{3SA} mice with mice that expressed a tagged *Myc* cDNA inserted upstream of the immunoglobulin heavy chain enhancer (*iMyc*$^{E\mu}$; a common translocation in human Burkitt's lymphoma), and found that expression of MDM4-3SA significantly accelerated lymphomagenesis. Using age-matched pre-tumour littermates the authors found that the levels of apoptosis were mostly unchanged, but that expression of MDM4-3SA resulted in an increased proportion of cells in S phase with activated DNA damage response signalling. Moreover, unlike tumours from *iMyc*$^{E\mu}$ mice, in which the p53 pathway is often mutated, tumours from *Mdm4*^{3SA};*iMyc*$^{E\mu}$ mice did not have mutated p53, indicating that MDM4 phosphorylation and degradation is important for the full activation of the p53 response to the effects of oncogene-induced hyper-proliferation.

These data demonstrate that post-translational modifications of MDM4 are important for increased p53 activity in response to DSBs and oncogene hyperactivation and therefore for the suppression of tumorigenesis. These data also indicate that inhibiting MDM4 phosphorylation or degradation could be protective in normal tissues during radiotherapy.

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ORIGINAL RESEARCH PAPER Wang, Y. V. *et al.* Increased radioresistance and accelerated B cell lymphomas in mice with Mdmx mutations that prevent modifications by DNA-damage-activated kinases. *Cancer Cell* **16**, 33–43 (2009)