Nature Reviews Molecular Cell Biology | AOP, published online 17 November 2010; doi:10.1038/nrm3017

OXIDATIVE STRESS

ATM bonds under stress

> a novel pathway for ATM activation and ... evidence that ATM acts as an oxygen sensor in human cells.

The protein kinase ataxia telangiectasia (A-T) mutated (ATM) mediates the cellular response to DNA damage by phosphorylating several key proteins, leading to cell cycle arrest, DNA repair or apoptosis. ATM can also be activated under conditions of oxidative stress, resulting in apoptosis or cell cycle arrest. It has become evident that these two responses are regulated by alternative mechanisms. In a study published in *Science,* Paull and colleagues have characterized a novel pathway for ATM activation and provide evidence that ATM acts as an oxygen sensor in human cells.

In response to DNA damage, non-covalently associated dimeric ATM is converted to an active monomer by the MRE11A–RAD50–NBS1 (MRN) DNA repair complex. ATM then phosphorylates proteins that initiate activation of the DNA damage response, including p53 and Ser/Thr-protein kinase CHK2. In a twist of this general scheme, the authors show that oxidative stress-mediated activation of ATM is independent of the MRN complex and affects only a subset of the ATM targets that are induced downstream of DNA damage.

Interestingly, they also found that activation of ATM by H_2O_2 was strongly inhibited by reducing agents and that promotion of disulphide bonds within ATM was sufficient to activate ATM in the absence of reactive oxygen species. Analysis of ATM by SDS–PAGE revealed that, unlike the DNA damage response (in which ATM is active as a monomer), oxidative stress induced the formation of covalent dimers containing autophosporylated ATM.

Are disulphide bonds essential for ATM activation by oxidative stress? The authors determined that a disulphide bond was formed at a crucial cysteine residue, Cys2991. Mutation of this residue (C2991L) specifically blocked activation through the oxidation pathway, but not in response to DNA damage. To test for functional relevance, wild-type ATM and C2991L-mutant ATM were induced in lymphoblasts that were isolated from a patient with A-T who lacked functional ATM. Cells expressing wild-type ATM showed a strong apoptotic response to both H_2O_2 and camptothecin (a drug that induces DNA breaks), whereas cells expressing mutant ATM responded only to camptothecin. Also, C2991L-mutant ATM that was ectopically expressed in cells with wild-type ATM functioned as a dominant-negative, emphasizing the Cys-mediated cooperation between monomers that is necessary for ATM's participation in the oxidative-stress response.

Collectively, these results show that oxidation of ATM directly induces ATM activation in the absence of DNA damage and the MRN complex. The authors propose that ATM may regulate the global cellular responses to oxidative stress.

GETTY

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NCI–Nature Pathway Interaction Database

ORIGINAL RESEARCH PAPER Guo, Z. *et al.* ATM activation by oxidative stress. *Science* **330**, 517–521 (2010)
FURTHER READING Lanvin, M. F. Ataxia-telangiectasia: from a rare disorder to a paradigm for cell signalling and cancer. *Nature Rev. Mol. Cell Biol.* **9**, 759–769 (2008)