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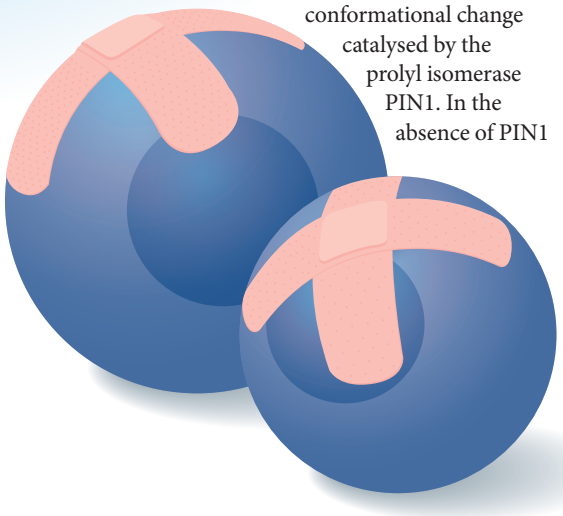
DNA DAMAGE RESPONSE

ATR prevents premature apoptosis

> the UV light-induced ATR-H *cis*-conformation has a direct anti-apoptotic role in mitochondria

The crucial nuclear role of the checkpoint kinase ATR in the DNA damage response is complemented by a mitochondrial role as an anti-apoptotic factor, according to new research published in *Molecular Cell*. Thus, following DNA damage, ATR has a dual function in promoting cell survival for long enough to enable DNA repair.

Western blot analysis showed that UV light-induced DNA damage results in an electrophoretic mobility shift of cytoplasmic, but not nuclear, ATR — from what the authors designate the ATR-L form to the ATR-H form. This shift was not caused by post-translational modification but was instead shown to reflect a conformational change catalysed by the prolyl isomerase PIN1. In the absence of PIN1 catalytic activity, cytoplasmic ATR was predominantly of the ATR-H *cis*-conformation, even in the absence of UV irradiation. The results suggest that PIN1 maintains the ATR-L *trans*-conformation under normal conditions. This was confirmed in an *in vitro* isomerization assay, which further showed that phosphorylation of ATR-H is required for PIN1 binding, and that UV irradiation leads to the phosphorylation and inactivation of PIN1 and possibly to the dephosphorylation of ATR-H.



Vicky Summersby/NPG

The combined effect of UV irradiation is therefore to prevent PIN1-mediated ATR-H to ATR-L isomerization. Following UV irradiation, the accumulated cytoplasmic ATR-H was localized exclusively to the mitochondrial outer membrane through direct interaction with the apoptotic protein BID. ATR contains three potential BH3-like domains, of which the second domain (amino acids 462–474) was required for ATR-H–BID interaction. The PIN1-induced isomerization of ATR-H to ATR-L results in a conformational change of the amino-terminal region of ATR that is thought to sequester this BH3-like domain and prevent binding to BID.

The pro-apoptotic protein BAX is known to be activated by its binding to truncated BID (tBID) on mitochondria, resulting in cytochrome *c* release and apoptosis. However, the accumulation of BID on mitochondria after UV irradiation was accompanied by BAX accumulation only in the absence of ATR, which suggests that BID binding by ATR-H might prevent BAX–tBID interactions. In line with this, ATR-H significantly decreased cytochrome *c* release from isolated mitochondria incubated with tBID. The survival of UV-irradiated cells was decreased by mutating the BH3-like domain of ATR and was increased by PIN1 depletion. Of note, these mitochondrial effects of ATR are independent of its kinase activity and its nuclear co-factor ATRIP.

Together, the data indicate that the UV light-induced ATR-H *cis*-conformation has a direct anti-apoptotic role in mitochondria by preventing the activation of BAX. This could prolong cell survival while (nuclear ATR-mediated) DNA repair is attempted. In healthy cells, PIN1 converts ATR-H to ATR-L, which allows for BAX-mediated apoptosis in response to appropriate signals.

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ORIGINAL RESEARCH PAPER Hilton, B. A. *et al.* ATR plays a direct antiapoptotic role at mitochondria, which is regulated by prolyl isomerase Pin1. *Mol. Cell* http://dx.doi.org/10.1016/j.molcel.2015.08.008 (2015)