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IN BRIEF

AUTOPHAGY

Chaperone-mediated autophagy degrades CHK1

During chaperone-mediated autophagy (CMA), substrates destined for degradation are recognized by heat shock cognate 70 (HSC70), which transfers them to the receptor lysosome-associated membrane protein 2A (LAMP2A) for translocation into the lysosome. Park *et al.* identify checkpoint kinase 1 (CHK1) as a target of CMA following genotoxic stress. LAMP2A-null cells had higher levels of nuclear CHK1 and DNA damage in response to damaging agents; increased levels of CHK1 enabled DNA damage to accumulate by preventing cell cycle progression. In control cells, CHK1 was degraded by CMA, as judged by its association with lysosomes and HSC70, and its increased levels when lysosomal activity was blocked. Inhibiting nuclear export reduced CHK1 degradation following etoposide treatment, suggesting that nuclear CHK1 is degraded by CMA following DNA damage. As preventing CMA, and thus increasing nuclear CHK1 levels, destabilized the DNA repair complex MRN (MRE11–RAD50–NBS1), CMA-mediated CHK1 degradation might protect cells against genotoxic stress.

ORIGINAL RESEARCH PAPER Park, C., Suh, Y. & Cuervo, A. M. Regulated degradation of Chk1 by chaperone-mediated autophagy in response to DNA damage. *Nature Commun.* **6**, 6823 (2015)

PROTEIN FOLDING

Drugs for protein misfolding diseases

Phosphorylation of eukaryotic translation initiation factor 2α (eIF2α) helps to prevent the accumulation of misfolded proteins in the endoplasmic reticulum by decreasing protein synthesis; this phosphorylation is removed by a complex composed of the phosphatase PP1c and its regulatory subunit PPP1R15A. Although the compound guanabenz (GBZ) inhibits PPP1R15A–PP1c, it is unsuitable for *in vivo* use, as it has affinity for the α2-adrenergic receptor. Das *et al.* show that the GBZ derivative Sephin1 overcomes this limitation. Sephin1 bound to PPP1R15A, but not to PPP1R15B, *in vitro* and disrupted PPP1R15A–PP1c, but not PPP1R15B–PP1c, *in vivo*, validating its specificity. Importantly, Sephin1 has no affinity for the α2-adrenergic receptor, and mice treated with it do not show the side effects associated with GBZ. Instead, Sephin1 reversed disease symptoms in mouse models of two protein-misfolding diseases — Charcot–Marie–Tooth 1B and amyotrophic lateral sclerosis.

ORIGINAL RESEARCH PAPER Das, I. *et al.* Preventing proteostasis diseases by selective inhibition of a phosphatase regulatory subunit. *Science* **348**, 239–242 (2015)

DNA DAMAGE RESPONSE

Taking the DDR down a Notch

The Notch signalling pathway regulates cell fate determination and can promote tumorigenesis. Vermezovic *et al.* found that the NOTCH1 receptor suppresses the activation of the DNA damage response (DDR) in nematodes and in human cells by inhibiting the kinase ataxia telangiectasia mutated (ATM). This required the nuclear localization of NOTCH1 but not its transcriptional activity, as cells with transcriptionally inactive NOTCH1 could inhibit ATM activation. NOTCH1 directly binds to the ATM regulatory domain FATC to inhibit its kinase activity. Furthermore, NOTCH1 inhibition promoted ATM-dependent apoptosis in irradiated acute lymphoblastic leukaemia cells, in which NOTCH1 has an oncogenic role, and ATM and NOTCH1 activities were inversely correlated in human breast cancers.

ORIGINAL RESEARCH PAPER Vermezovic, J. *et al.* Notch is a direct negative regulator of the DNA-damage response. *Nature Struct. Mol. Biol.* **22**, 417–424 (2015)