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CELL SIGNALLING

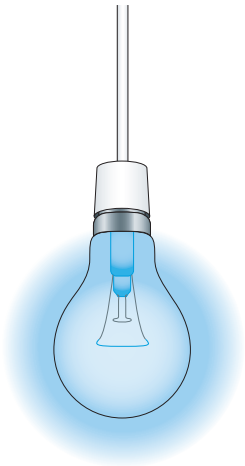
DNA damage puts p38 under the UV light

Ultraviolet radiation (UVR) forms bulky DNA adducts that interfere with transcription and RNA metabolism. However, how UVR-induced signalling pathways regulate gene expression is poorly understood. Borisova *et al.* now show that UVR-induced signalling by MAP kinase p38 alpha (p38; also known as MAPK14) promotes transcription elongation at damage-response genes.

UVR transiently activated p38 in human cell lines, and inhibition of p38 compromised cell survival following UVR. Using quantitative mass spectrometry-based proteomics, the authors identified 138 sites in 122 proteins, many of them involved in transcription and RNA binding, that were phosphorylated in a p38-dependent manner following UVR.

The phosphorylation sites did not occur within the p38 phosphorylation motif. Indeed, depletion or inhibition of MAPK-activated protein kinase 2 (MK2) and MK3, which function downstream of p38, abolished phosphorylation in 60% of these sites. Thus, MK2 and MK3 are key transducers of UVR-induced p38 signalling. UVR-induced MK2-dependent phosphorylation was previously shown to serve as a platform for recruiting 14-3-3 proteins, which are downstream effectors of several signalling pathways. Notably, nearly 30% of the proteins that interacted with 14-3-3 following UVR did so in a p38-dependent manner.

One of the p38–MK2 substrates was negative elongation factor E (NELFE). NELFE is the RNA-binding component of the NELF complex, which inhibits transcription elongation by RNA polymerase II (Pol II). Following UVR, MK2 phosphorylated eight NELFE Ser residues, three of which were in 14-3-3 binding motifs and interacted with different 14-3-3 proteins. Of these, Ser115 phosphorylation was especially necessary for 14-3-3 binding.



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> “UVR induces p38–MK2-dependent phosphorylation of… NELFE”

Following UVR, all NELF components rapidly dissociated from the chromatin in a p38-dependent manner. ChIP-seq analysis of Pol II revealed that UVR caused release of Pol II from promoter-proximal pausing into productive transcription elongation at >2,000 genes, many of which are involved in RNA metabolism and the DNA damage response. Importantly, NELFE is known to bind 70% of these genes.

In summary, UVR induces p38–MK2-dependent phosphorylation of RNA-binding proteins, including NELFE. Dissociation of NELFE from chromatin, possibly through 14-3-3 binding, promotes Pol II transcription elongation and could be essential for cell recovery from UVR.

Eytan Zlotorynski

ORIGINAL ARTICLE Borisova, M.E. *et al.* p38-MK2 signaling axis regulates RNA metabolism after UV-light-induced DNA damage. *Nat. Commun.* **9**, 1017 (2018)