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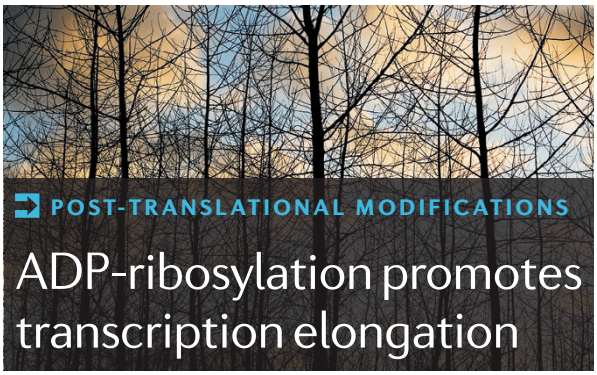

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POST-TRANSLATIONAL MODIFICATIONS

ADP-ribosylation promotes transcription elongation

Poly(ADP-ribose) polymerases (PARPs) comprise a large family of ADP-ribosyl transferases that covalently link ADP-ribose molecules, derived from oxidized nicotinamide adenine dinucleotide (NAD^+), to proteins of diverse functions. Specifically, PARP1, PARP2 and PARP3 have roles in DNA damage repair and gene expression; a study by Gibson *et al.* now shows that PARP1 also promotes transcription elongation.

The authors developed a new method to distinguish between ADP-ribosylation targets of individual PARPs, based on PARP mutants with intact enzymatic activity that are sensitive to (can use) specialized NAD^+ analogues (asPARP). The authors engineered asPARP1, asPARP2 and asPARP3 enzymes, and chemically modified a NAD^+ analogue to facilitate asPARP-selective ADP-ribosylation as well as 'click' chemistry reactions for the labelling or purification of target proteins.

To identify site-specific PARP targets in human cells, asPARP1, asPARP2 or asPARP3 and the NAD^+ analogue were incubated with nuclear extracts. The clicked NAD^+ analogue-labelled proteins were purified and analysed, revealing unique as well as overlapping PARP1, PARP2 and PARP3 targets. Two of the identified PARP1 targets are negative elongation factor A (NELFA) and NELFE, subunits of the NELF complex, which inhibits transcription elongation by stimulating the pausing of RNA polymerase II (Pol II) close to transcription start sites.

Interestingly, known phosphorylation sites are frequently found at or near the identified ADP-ribosylation sites, which indicates functional interactions between these post-translational modifications. Indeed, ADP-ribosylation of NELFE depended on the activity of cyclin-dependent kinase 9 (CDK9). Genome-wide, PARP1-mediated ADP-ribosylation was enriched at the promoters of transcriptionally active genes, and this as well as CDK9 occupancy at promoters strongly correlated with low levels of Pol II pausing. PARP1 knockdown or inhibition increased Pol II pausing and reduced productive elongation, which was reversed by a viral NELF inhibitor. Finally, mutating the ADP-ribosylation site of NELFE produced a NELF complex that is resistant to inhibition by PARP1 and is a more potent inducer of Pol II pausing. Thus, PARP1-dependent ADP-ribosylation of NELF proteins promotes transcription elongation.

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ORIGINAL ARTICLE Gibson, B. A. *et al.* Chemical genetic discovery of PARP targets reveals a role for PARP-1 in transcription elongation. *Science* http://dx.doi.org/10.1126/science.aaf7865 (2016)

FURTHER READING Jonkers, I. & Lis, J. T. Getting up to speed with transcription elongation by RNA polymerase II. *Nat. Rev. Mol. Cell Biol.* **16**, 167–177 (2015)