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POST-TRANSLATIONAL MODIFICATION

NRMT organizes methyl transfer

> NRMT is an α-N-methyltransferase for RCC1.

Although the post-translational methylation of α-amino groups (α-N-methylation) was discovered over 30 years ago, little was known about its mechanism and function. Indeed, the only known function of α-N-methylation is its requirement by the Ran guanine nucleotide exchange factor RCC1 for normal cell mitosis. Macara and colleagues now describe the first eukaryotic α-N-methyltransferase, named N-terminal RCC1 methyltransferase (NRMT) for its ability to modify RCC1, and identify several new α-N-methylation targets as a result of this discovery.

The authors assessed HeLa cell nuclear fractions for protein methylation and analysed the fraction that methylated RCC1 using mass spectrometry. They identified an uncharacterized methyltransferase called METTL11a, a member of the methyltransferase 11 family, which they rename NRMT. Overexpression of NRMT in cells increases RCC1 α-N-methylation on the N-terminal Ser, whereas depleting NRMT decreases this, confirming that NRMT is an α-N-methyltransferase for RCC1. The authors sought to gain insight into the function of this modification by examining the distribution of RCC1 in NRMT-depleted cells. Less RCC1 is associated with chromatin in cells lacking NRMT, and NRMT-depleted cells in mitosis exhibit ~3 times more supernumerary spindles than controls. These data suggest that RCC1 α-N-methylation stabilizes its association with chromatin to ensure proper mitotic division.

The structure of NRMT in complex with *S*-adenosylhomocysteine (SAH; which results from the transfer of the methyl group from *S*-adenosylmethionine to small molecules) was resolved at 1.75 Å by the Structural Genomics Consortium. This revealed a large cavity opposite the SAH-binding site that can accommodate N-terminal peptides. Using computer software the authors modelled an RCC1 N-terminal peptide (Ser-Pro-Lys-Arg-Ile-Ala) in the NRMT putative active site, and this suggested that only the first three residues of this motif interact with NRMT. Indeed, mutational analyses confirm that the motif X-Pro-Lys is important for substrate recognition by NRMT.

So, can the NRMT recognition sequence be used to identify new targets of α-N-methylation? The authors searched GenBank for NRMT candidate substrates using Met-(Ala/Ser/Pro)-Pro-Lys and also screened mouse tissues for α-N-methylation targets using methylation-specific antibodies. Notable predicted substrates from these analyses include the nuclear oncogene SET (also known as TAFI and PHAPII) and the tumour suppressor retinoblastoma (RB). Recombinant NRMT can methylate the N-terminal tail of both SET and RB *in vitro*. Furthermore, when NRMT is depleted from cells, SET and RB methylation is substantially reduced. Thus, SET and RB are novel α-N-methylated proteins and NRMT is the enzyme that catalyzes this modification.

In short, this study identifies NRMT as the eukaryotic α-N-methyltransferase and uses this knowledge to provide further insight into the function of RCC1 α-N-methylation and to identify two new α-N-methylation targets, and more than 35 putative targets, for further analysis.

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GETTY

ORIGINAL RESEARCH PAPER Schaner Tooley, C. E. *et al.* NRMT is an α-N-methyltransferase that methylates RCC1 and retinoblastoma protein. *Nature* 28 July 2010 (doi:10.1038/nature09343)

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