Arginine methylation in subunits of mammalian pre-mRNA cleavage factor I

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Mammalian cleavage factor I (CF Im) is composed of two polypeptides of 25 kDa and either a 59 or 68 kDa subunit (CF Im25, CF
Im59, CF Im68). It is part of the cleavage and polyadenylation complex responsible for processing the 39 ends of messenger RNA
precursors. To investigate post-translational modifications in factors of the 39 processing complex, we systematically searched
for enzymes that modify arginines by the addition of methyl groups. Protein arginine methyltransferases (PRMTs) are such
enzymes that transfer methyl groups from S-adenosyl methionine to arginine residues within polypeptide chains resulting in
mono- or dimethylated arginines. We found that CF Im68 and the nuclear poly(A) binding protein 1 (PABPN1) were methylated
by HeLa cell extracts in vitro. By fractionation of these extracts followed by mass spectral analysis, we could demonstrate that
the catalytic subunit PRMT5, together with its cofactor WD45, could symmetrically dimethylate CF Im68, whereas pICln, the
third polypeptide of the complex, was stimulatory. As sites of methylation in CF Im68 we could exclusively identify arginines in
a GGRGRGRF or “GAR” motif that is conserved in vertebrates. Further in vitro assays revealed a second methyltransferase,
PRMT1, which modifies CF Im68 by asymmetric dimethylation of the GAR motif and also weakly methylates the C-termini of
both CF Im59 and CF Im68. The results suggest that native—as compared with recombinant—protein substrates may contain
additional determinants for methylation by specific PRMTs. A possible involvement of CF Im methylation in the context of RNA
export is discussed.

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