S1 | The mammalian DNA methylation machinery. The mammalian DNA methylation machinery is a two-component system. DNA methyltransferases establish and maintain methylation marks, while methyl-CpG binding proteins interpret these marks.

DNA methyltransferase	**Function**	**Localization**	**Activity**
DNMT1	Maintenance of methylation, repression of transcription[1–3]	Replication foci in S-phase[4]	Preference for hemi-methylated DNA[5]
DNMT2	Unknown	Nuclear, not well characterized	Low activity *in vitro*[6]
DNMT3A	Methylation remodeling during embryogenesis, imprint establishment[7], repression[8]	Heterochromatin and nucleoplasm[8]	*De novo* methylation[5]
DNMT3B	Methylation remodeling during embryogenesis, repeat methylation[9], repression[8]	Heterochromatin and nucleoplasm[8,10]	*De novo* and maintenance methylation
DNMT3L	Methylation remodeling during embryogenesis, imprint establishment, spermatogenesis[11], repression[12]	Heterochromatin and nucleoplasm	Not an active enzyme
Methyl-CpG binding protein	**Function**	**Repression mediated by:**	**Binding Specificity**
MeCP2	Transcriptional repression	SIN3A, HDAC complex [13,14]	Single symmetrically methylated CpGs
MBD1	Transcriptional repression	Partially HDAC-dependent repression[15]	Methylated and unmethylated DNA
MBD2	Transcriptional repression	MeCP1 chromatin remodeling complex[16]	Methylated DNA
MBD3	Transcriptional repression	NuRD chromatin remodeling complex[17,18]	Unmethylated DNA
MBD4	DNA repair, glycosylase domain, repair of deaminated 5-methyl C[19]	NA	$^{5\text{-methyl}}$CpG/TpG mismatches

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