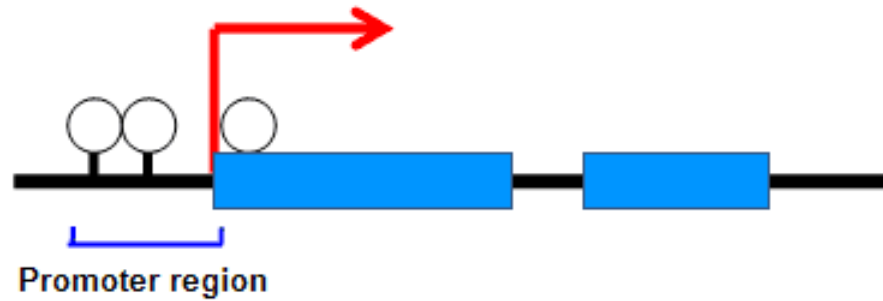
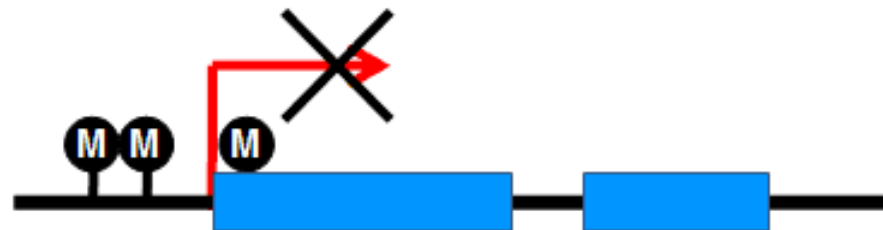


Genes that can be expressed



Genes inactivated by DNA methylation



● M Methylated

○ Unmethylated

Fig. 1. Inactivation of a gene by DNA methylation.

When a promoter region is methylated, the gene cannot be expressed.

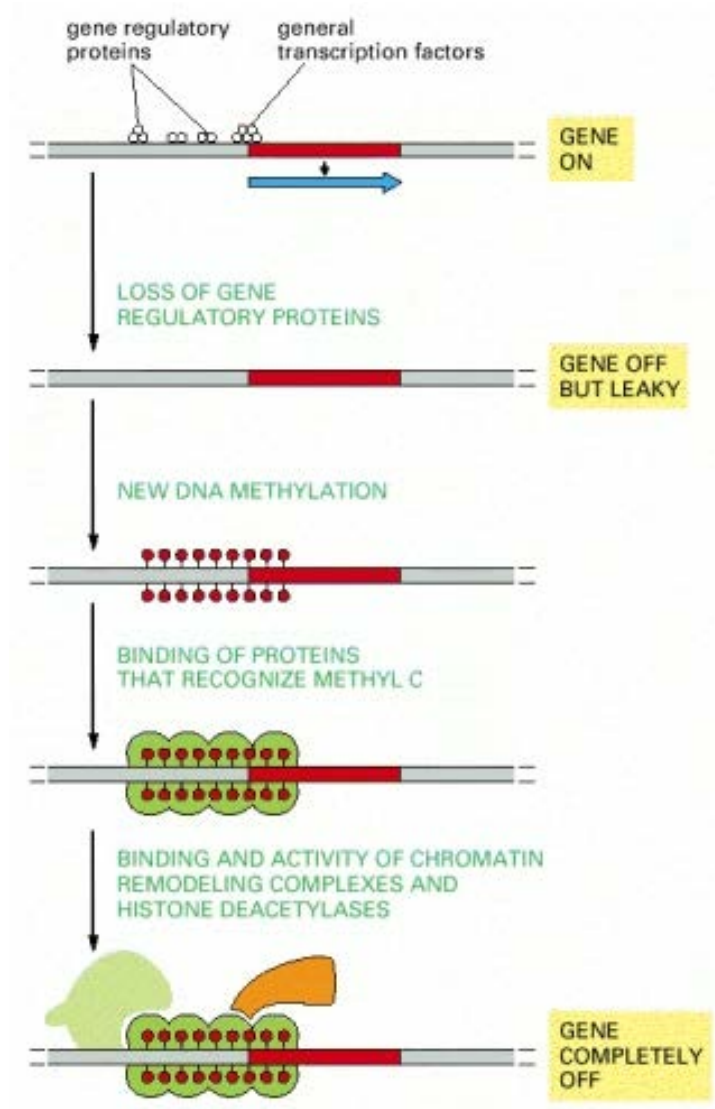
The Molecular Biology of the Cell

Figure 7-82

How DNA methylation may help turn off genes

The binding of **gene regulatory proteins** and the general transcription machinery near an active **promoter** may prevent **DNA methylation** by excluding *de novo* methylases. If most of these **proteins** dissociate from the DNA, however, as generally occurs when a cell no longer produces the required activator **proteins**, the DNA becomes methylated, which enables other **proteins** to bind, and these shut down the **gene** completely by further altering chromatin structure

Additional possible mechanisms of gene silencing shown on next page



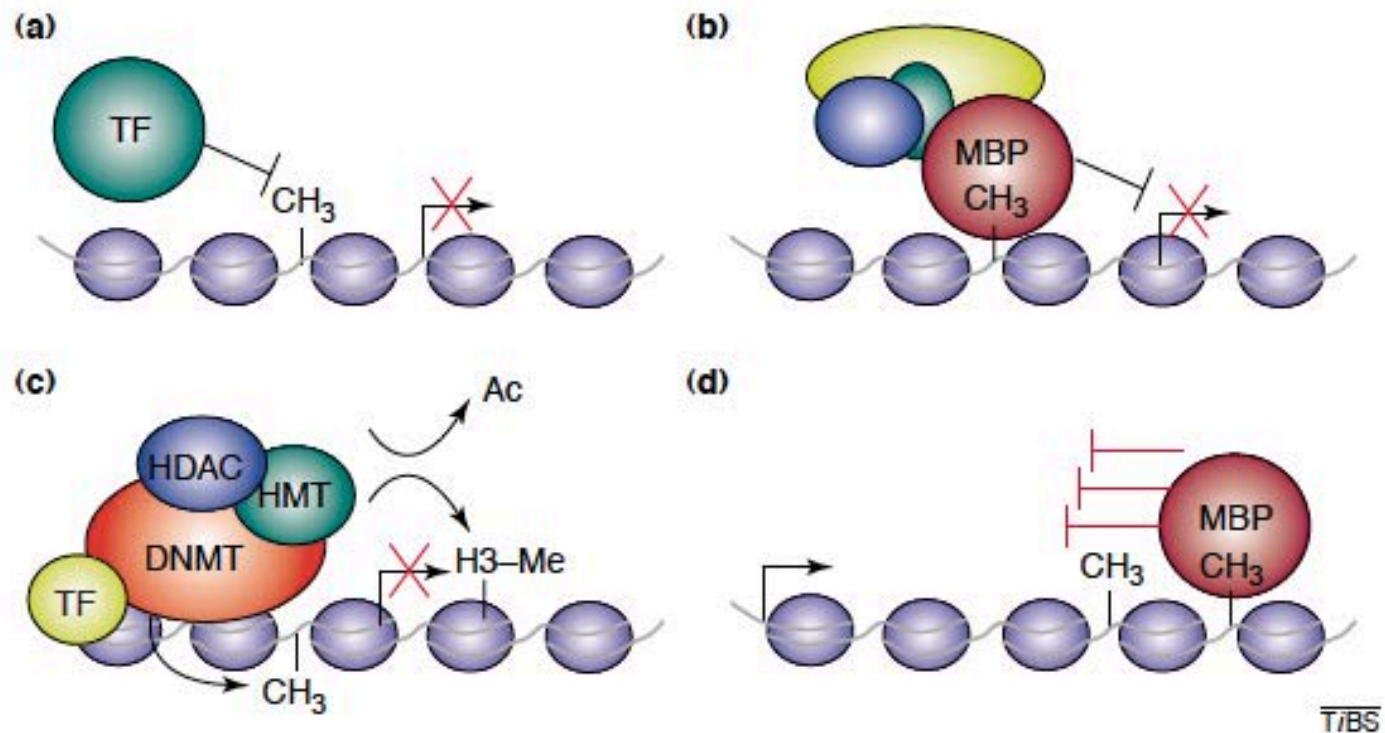
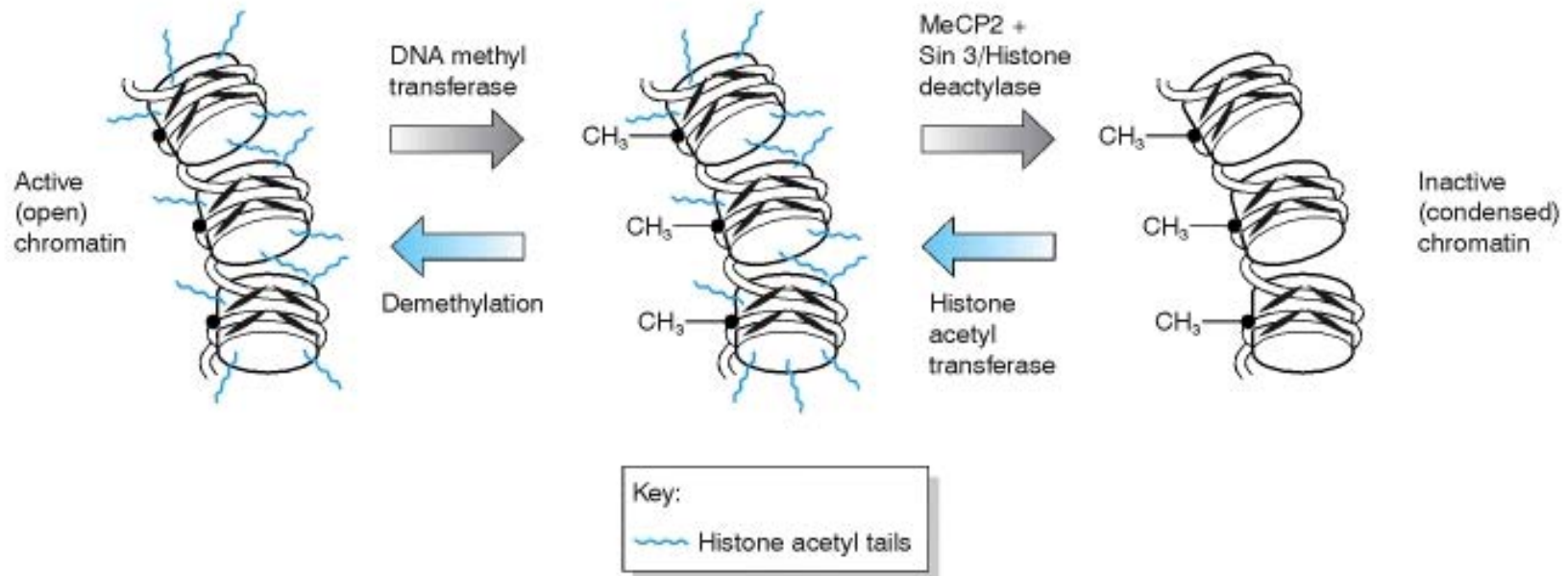


Figure 2. Mechanisms of DNA-methylation-mediated repression. (a) DNA methylation in the cognate DNA-binding sequences of some transcription factors (TF) can result in inhibition of DNA binding. By blocking activators from binding targets sites, DNA methylation directly inhibits transcriptional activation. (b) Methyl-CpG-binding proteins (MBPs) directly recognize methylated DNA and recruit co-repressor molecules to silence transcription and to modify surrounding chromatin. (c) In addition to their DNA methyltransferase activities, DNMT enzymes are also physically linked to histone deacetylase (HDAC) and histone methyltransferase (HMT) activities. In this case, the addition of methyl groups to DNA is coupled to transcriptional repression and chromatin modification. (d) DNA methylation within the body of genes can also have a dampening effect on transcriptional elongation. MBPs might be involved in inhibiting elongation, either directly or by their effects on the surrounding chromatin structure.

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Figure 8.21 Transcriptional repression by histone deacetylation may be mediated by DNA methylation CpG dinucleotides are targets for DNA methylation and, in turn, methylated CpGs are targets for specific binding by proteins such as MeCP2, which acts as a transcriptional repressor and recruits a corepressor complex consisting of the transcription factor repressor mSin3A and histone deacetylases. The latter removes acetyl groups from histones. The reverse process involves sequential histone acetylation then DNA demethylation (see Ng and Bird, 1999).



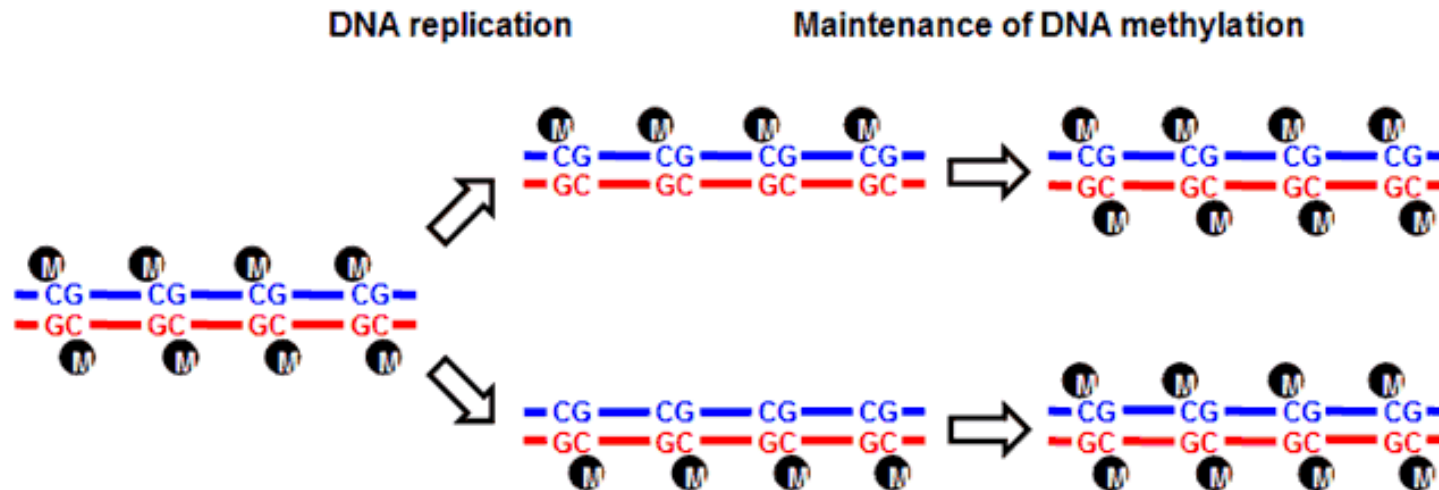
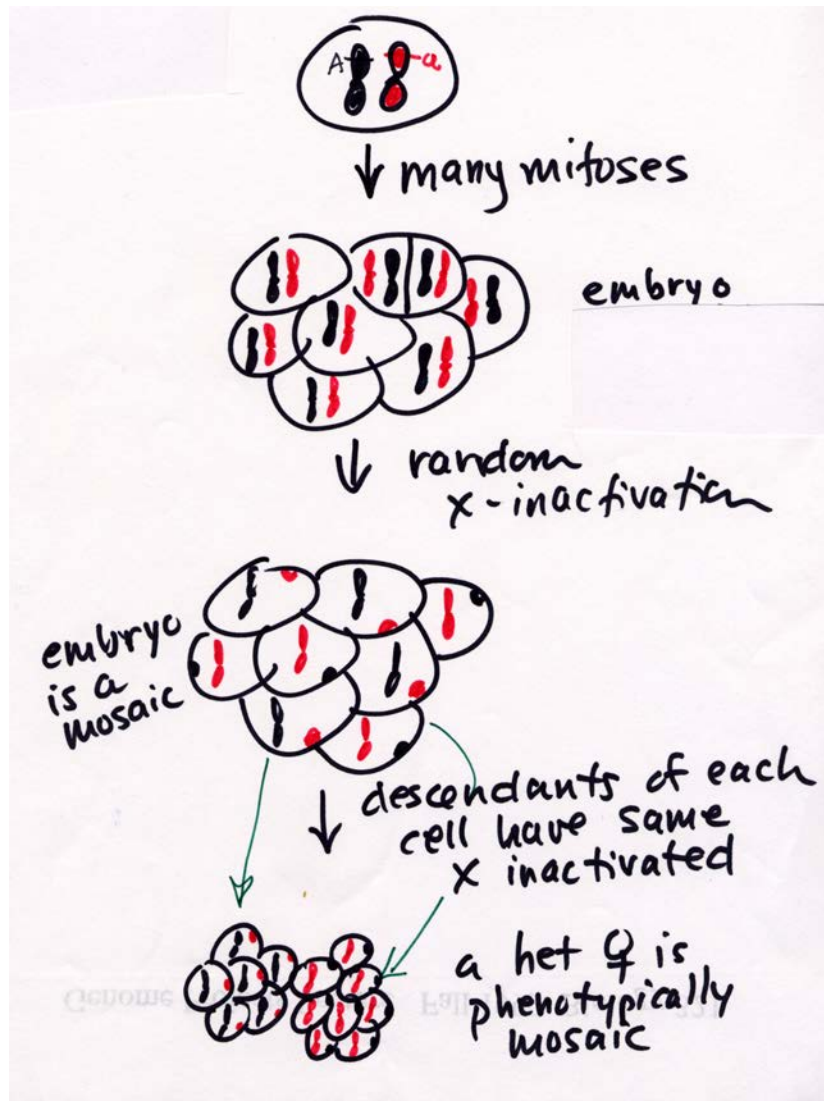


Fig. 2. Maintenance of DNA methylation status

When cells divide, DNA is replicated. Although the newly synthesized DNA strands are unmethylated, DNA methyltransferase 1 (DNMT1) precisely maintains the DNA methylation status.

Female embryo heterozygous (Aa) for an X-linked gene



- **X-chromosome inactivation** occurs when the embryo has hundreds of cells
- This an epigenetic event: the inactivated X chromosome is heavily methylated and highly condensed
- Mitotic descendants of a given cells have the same X copy of the X inactivated



The calico cat is heterozygous for the X-linked pigment gene and carries a dominant, autosomal white-spotting mutation