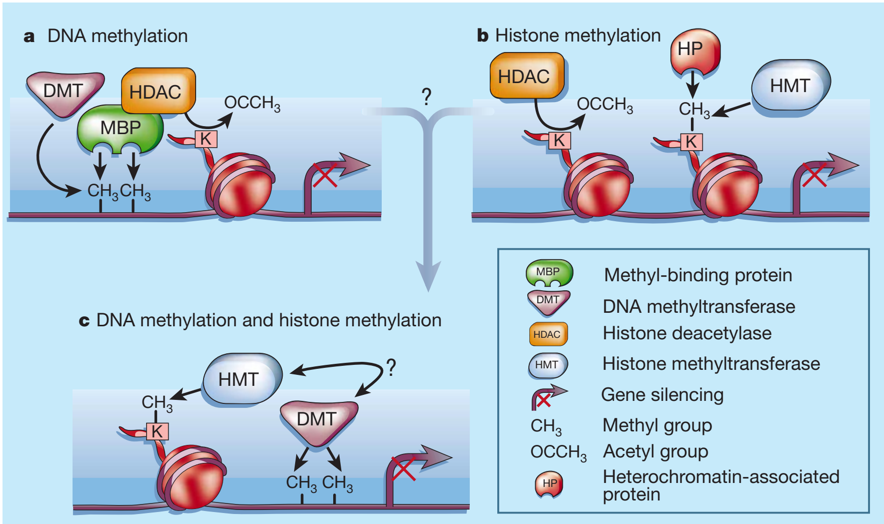

Figure 1 **Methylation-associated models of gene silencing.** a, **DNA methylation. Cytosine nucleotides are methylated by a DNA methyltransferase, increasing the affinity of methyl-binding proteins for DNA. Some of these proteins associate with repressive complexes that contain histone deacetylases, resulting in the removal of acetyl groups from lysine (K) residues in the tails of histone proteins, and gene silencing.** b, **Histone methylation. Acetyl groups must be removed before lysine residue 9 on histone H3 can be methylated by a histone methyltransferase. Heterochromatin-associated proteins preferentially bind methylated lysine 9, leading to gene silencing.** c, **DNA methylation and histone methylation. Tamaru and Selker[1] show that methylation of histone H3 lysine 9 is required for subsequent DNA methylation and gene silencing in filamentous fungi. It is not known whether or not the histone and DNA methyltransferases interact.**

gene resulted in cell death. Interestingly, though, mutation of this amino acid had no noticeable effect on another type of fungus, *Saccharomyces cerevisiae*[7], and indeed the methylation of DNA and of histone H3 lysine 9 has not been detected in this species[8]. This implies that the histone- and DNA-methylation-dependent mechanism of gene silencing may not apply to all organisms.

That message was also clear from the discovery that a silencing pathway using histone methylation can function independently of DNA methylation[6]. Fruitflies (*Drosophila melanogaster*) and another yeast, *Schizosaccharomyces pombe*, have no known regions of DNA methylation in their genomes. In these organisms, gene silencing is associated with histone deacetylation and histone methylation followed by the binding of a repressive protein (a 'heterochromatin-associated protein'; Fig. 1b)[6,9,10]. Such repressive proteins are typically localized to silent regions of the genome[11].

By contrast, the DNA-methylation silencing pathway has not yet been found to work independently of histone methylation, supporting Tamaru and Selker's proposal[1] that histone methylation is required for DNA methylation. As yeast and many invertebrates do not typically have DNA methylation, perhaps this phenomenon evolved with histone methylation to add another layer of gene regulation in more complex genomes (Fig. 1c).

We predict that the mechanisms of gene silencing in humans are hybrids of the models illustrated in Fig. 1. But these models may not be mutually exclusive in any species. For example, DNA methylation is not used to silence many of the genes that are switched on and off in a periodic manner in the cell-division cycle. So, histone methylation may have a predominant or exclusive role in keeping these genes silent until required, as shown for the *cyclin E* gene[12] in human and other cells. In contrast, histone and DNA methylation in combination may be used to repress constitutively silenced genes, as Tamaru and Selker show. In female vertebrates, this type of silencing may also occur on the inactive X chromosome, where the methylation of both histone H3 lysine 9 and DNA is enriched (our unpublished results).

Tamaru and Selker's exciting results[1] show once again how important histone methylation is in the epigenetic control of gene expression. It will now be necessary to re-evaluate fundamental epigenetic concepts with respect to histone methylation, and to unravel exactly how DNA methylation and histone methylation interact. Will the histone and DNA methyltransferases associate in a repressive protein complex *in vivo*? Could methyl groups on histones recruit DNA methyltransferases, or do DNA methyl groups recruit histone methyltransferases? Perhaps more important, it remains to be seen whether this newly discovered mechanism of gene silencing takes place in humans. If so, there will certainly be many ramifications for human development and disease. ■

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NATURE

100 YEARS AGO

Photography for Naturalists. **The advantages of photography as compared with wood-engraving for the illustration of works on natural history are in many ways so great that any attempt to perfect and popularise the methods in use should be heartily welcomed. Quite apart from artistic effect, the great superiority of photography is that it ensures absolute accuracy, and, when living animals are the subjects, shows them in natural attitudes. In wood-engraving there are several sources of error which only too frequently make themselves apparent. In the first place, the draughtsman may make a blunder. But too often it is the engraver who is in fault, very frequently from mistaking the nature of some feature in the drawing he has to reproduce. For example, the author of the volume before us calls attention to a curious engraver's error in a well-known popular work, where, from some misconception, the mouth of a stickleback appears in a totally wrong position.**

From *Nature* 14 November 1901.

50 YEARS AGO

The progress of nuclear physics in the past two decades has depended greatly on the use of machines for producing high-energy particles; these fast particles are used for bombarding atomic nuclei with the aim of producing nuclear transformations. Though the first machines were built nearly twenty years ago, much still remains to be known about the atom. It must be remembered that we know today about nine hundred different kinds of atomic nuclei; only three hundred of them are found in Nature, while the remainder have to be prepared artificially, using either high-energy particles or neutrons coming from a nuclear pile. Furthermore, each of these nuclei is a complicated structure, with features many of which are still not understood. Finally, quite new phenomena have been recently discovered, such as the artificial creation of mesons in high-energy nuclear collisions. These mesons, previously found only in the cosmic radiation, can now be studied much more closely, and their study is thought to bear closely on the riddle of the 'nuclear forces', the forces whereby the particles in an atomic nucleus are held together… there are at least three kinds of mesons with different mass, each of them unstable and prone to transform itself within a small fraction of a second into two photons.

Otto Frisch

From *Nature* 17 November 1951.