<Further Development 03_05>

Mechanisms of DNA Methylation During Genomic Imprinting

As described in Chapter 3, methylated DNA is associated with stable DNA silencing either (1) by interfering with the binding of gene-activating transcription factors or (2) by recruiting repressor proteins that stabilize nucleosomes in a restrictive manner along the gene. The presence of a methyl group in the minor groove of DNA can prevent certain transcription factors from binding to the DNA, thereby preventing the gene from being activated (Watt and Molloy 1988).

For example, during early embryonic development in mice, the *Igf2* gene (for insulin-like growth factor) is transcribed only from the sperm-derived (paternal) chromosome 7. The egg-derived (maternal) *Igf2* gene does not function during embryonic development because the CTCF transcription factor ("CCCTC binding factor") is an inhibitor that can block the promoter from getting activation signals from enhancers. The CTCF protein binds to a region near the *Igf2* gene in females because this region is not methylated. Once bound, it prevents the maternally derived *Igf2* gene from functioning. In the paternally derived chromosome 7, the region where CTCF would bind is methylated. CTCF cannot bind, and the gene is not inhibited from functioning (Figure 1; Bartolomei et al. 1993; Ferguson-Smith et al. 1993; Bell and Felsenfeld 2000).

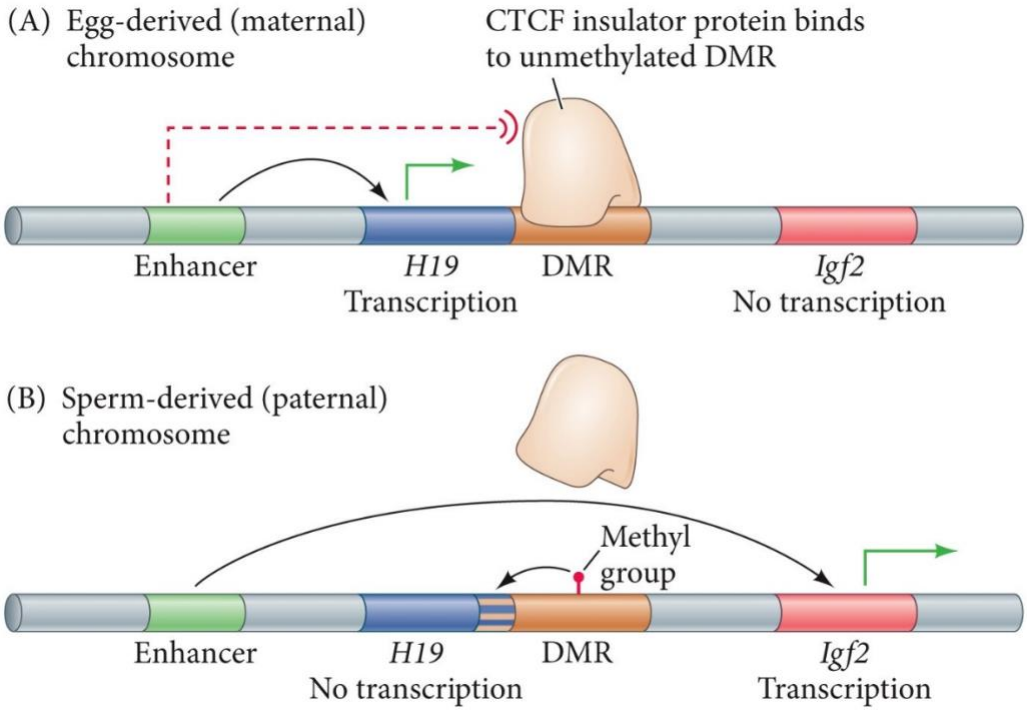

Figure 1 Regulation of the imprinted *Igf2* gene in the mouse. This gene is activated by an enhancer element it shares with the *H19* gene. The differentially methylated region (DMR) is a sequence located between the enhancer and the *Igf2* gene and is found on both sperm- and egg-derived chromosomes. (A) In the egg-derived chromosome, the DMR is unmethylated. The CTCF insulator protein binds to the DMR and blocks the enhancer signal. (B) In the sperm-derived chromosome, the DMR is methylated. The CTCF insulator protein cannot bind to the methylated sequence, and the signal from the enhancer is able to activate *Igf2* transcription.

In humans, misregulation of *IGF2* methylation causes Beckwith-Wiedemann growth syndrome. Although DNA methylation is the mechanism for imprinting this gene in both mice and humans, the mechanisms responsible for the differential *Igf2* methylation between sperm and egg appear to be very different in the two species (Ferguson-Smith et al. 2003; Walter and Paulsen 2003). Differential methylation is one of the most important mechanisms of epigenetic changes and is a reminder that an organism cannot be explained solely by its genes. One needs knowledge of developmental parameters (such as whether the gene was modified by the gamete transmitting it) as well as genetic ones.