

Epigenetics

Biosciences 741: Genomics

Fall, 2011

Week 9

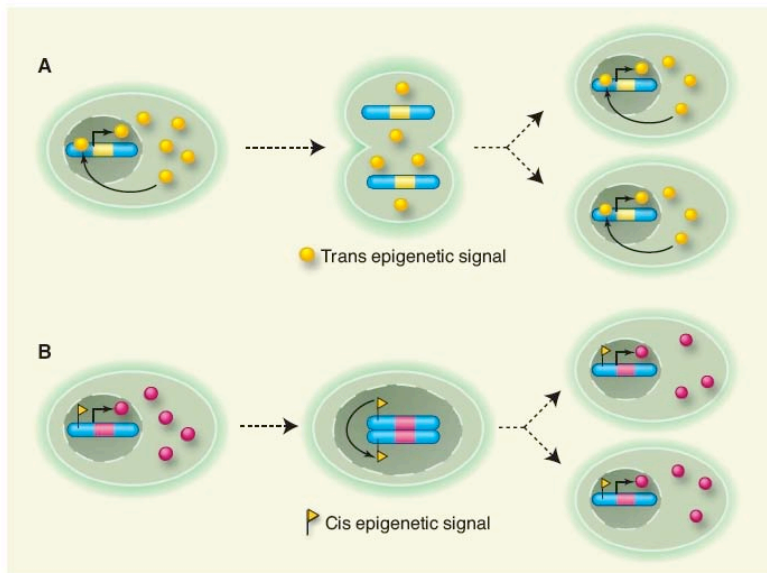
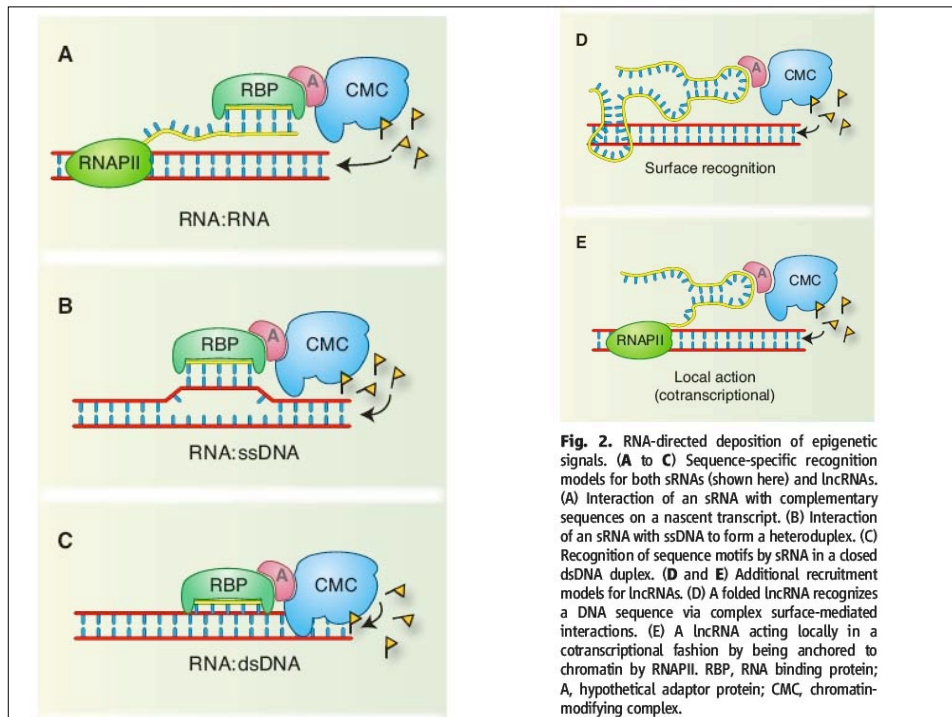


Fig. 1. Cis and trans epigenetic signals. **(A)** Trans epigenetic signals (yellow circles) are transmitted by partitioning of the cytosol during cell division and maintained by feedback loops. As an example, a simple regulatory loop in which the epigenetic signal induces its own expression is shown here. **(B)** Cis signals (yellow flags) are molecular signatures physically associated with the DNA and inherited via chromosome segregation during cell division.

Cis-acting epigenetic states

- Mono-allelic gene expression in diploid cells (olfactory receptors, immunoglobulins, etc).
- Imprinting (specific expression of the maternal vs. paternal allele).
- X-chromosome inactivation in female mammals.
- Cis-acting epigenetic states are characteristic of multicellular animals and plants, and are used to maintain distinct cell types.
- Cis epigenetic states may be initiated by induction of a transcription factor(s), microRNA(s), larger noncoding RNA(s), or some combination of the above.



Maintaining histone modifications

- Examples are known in which histone modifications are maintained by positive feedback loops (between the protein that binds to the modification & the enzyme that adds the modification).
- This may be responsible for the “spreading” of epigenetic states, as in *Drosophila* position-effect variegation.
- Histone modifications may also be maintained by cross-talk with DNA methylation.

Transmitting histone modifications

- It is not entirely clear how histone modifications are transmitted during DNA replication...
- However, transmission electron microscopy experiments have shown that the reformation of nucleosomes occurs immediately after the replication fork has passed, suggesting that nucleosome reassembly may be associated with the replication fork.
- In which case, the two-fold axis of symmetry of the nucleosome suggests the possibility that nucleosomes may be semi-conservatively replicated, hence preserving their modifications on each daughter chromatid.

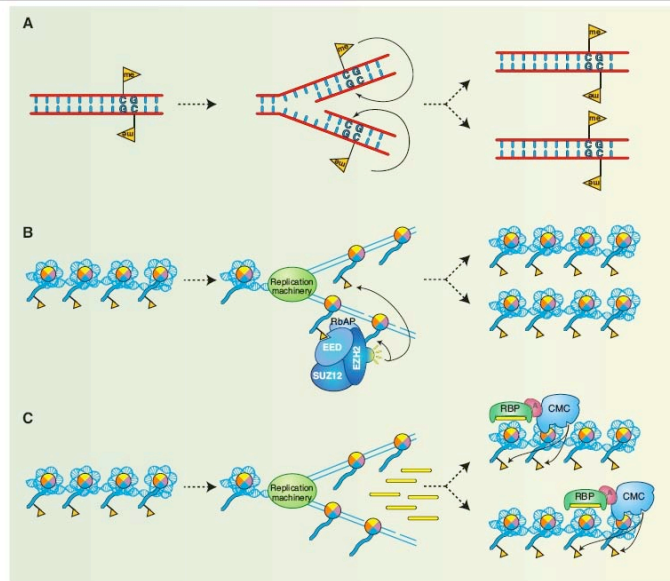


Fig. 3. Transmission of epigenetic states. (A) Transmission of DNA methylation patterns after DNA replication. (B) Hypothetical model for the maintenance of a histone-associated epigenetic signal, using H3K27me3 (yellow flags) as an example. H3K27me3 is diluted during DNA replication by the deposition of unmodified octamers. Binding of EED to H3K27me3 stimulates the enzymatic activity of EZH2, which places more H3K27me3 marks on neighboring nucleosomes, thus restoring a full epigenetic signature on both chromatids (32). (C) Maintenance of a chromatin domain via a secondary signal. S-phase transcription of heterochromatic repeats in *S. pombe* generates sRNA species that recruit chromatin-modifying complexes to reestablish heterochromatic signatures at the target loci.

Resetting epigenetic states during development

- At fertilization, the paternal genome is hyper-methylated, until a wave of DNA demethylation restores it to an active state (with the exception of some imprinted genes).
- During development, pluripotent germ cells undergo a second wave of DNA demethylation.
- Whether other cell types (i.e., neural stem cells) undergo additional waves of DNA demethylation is not yet clear, however it is clear that emotional experiences in early life can produce life-long DNA methylation in neuronal genes that influence behavior.

Discussion Questions

1. Lister et al. (2009) reported that CHH and CHG methylation showed enrichment in gene bodies and depletion in protein binding sites and enhancers. In what respects is this similar to, and in what respects is it different from, the patterns they found for CpG methylation?
2. How do stem cells and differentiated cells differ in terms of their patterns of DNA methylation? How do these differences correlate with the expression of specific DNA methyl transferases? (be specific: include gene names and whether their expression is increased or decreased in stem cells or differentiated cells) How could these differences in methyltransferase expression account for the observed differences in methylation patterns?
3. Explain how silent, primed, poised, and active genes differ from each other in terms of: (a) Epigenetic marks near the transcription start site; (b) Epigenetic marks at associated enhancer sites; (c) gene expression and gene function.