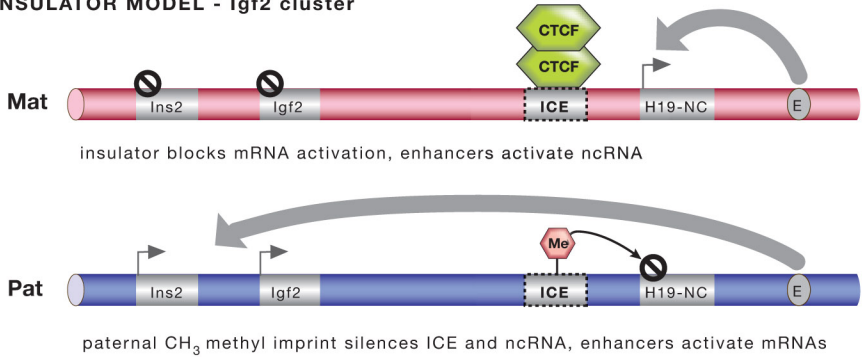


A. INSULATOR MODEL - *Igf2* cluster



B. ncRNA MODEL - *Igf2r* cluster

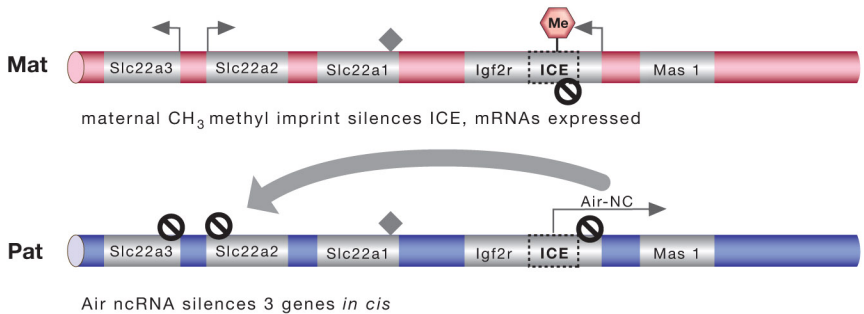


Figure 7. Two *cis*-Acting Silencing Mechanisms at Imprinted Gene Clusters

(a) Insulator model for the *Igf2* cluster. The expression pattern for endoderm is shown. On the maternal chromosome the unmethylated ICE binds the CTCF protein and forms an insulator that prevents the common endoderm enhancers (E) from activating *Igf2* and *Ins2*. Instead, the enhancers activate the nearby H19 ncRNA promoter. On the paternal chromosome, the methylated ICE cannot bind CTCF and an insulator does not form, hence the *Igf2* and *Ins2* mRNA genes are expressed only on this chromosome. The H19 ncRNA is methylated most likely because of spreading from the 2-kb distant methylated ICE, and silenced. (b) ncRNA model for the *Igf2r* cluster. The expression pattern for placenta is shown. On the maternal chromosome, the methylated ICE contains the Air ncRNA promoter that is directly silenced by the DNA methylation imprint. The *Igf2r*, *Slc22a2*, and *Slc22a3* mRNA genes are expressed only on this chromosome. *Mas1* and *Slc22a1* are not expressed in placenta. On the paternal chromosome, the Air ncRNA promoter lying in the unmethylated ICE is expressed, and silences *Igf2r*, *Slc22a2*, and *Slc22a3* *in cis*. Note that in both models, the DNA methylation imprint silences the ncRNA and permits mRNA expression. (ICE) Imprint control element, (gray box) imprinted mRNA gene, (gene-NC) imprinted ncRNA gene, (arrow) expressed allele of an activating gene, (black stop sign) repressed allele of an imprinted gene, (filled diamond) tissue-specific gene silenced on both parental chromosomes, (gray arrows) long-distance effect *in cis*.