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Genomic Imprinting and Mammalian development: A Genetic Arms Race

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Genomic imprinting is an epigenetic phenomenon by which the two parental alleles of a gene are differentially expressed. As of 1997 there are at least twenty genes known to be subject to genomic imprinting in mammals: five genes are maternally expressed and the remainder are paternally expressed. The laboratory has been studying the mechanism of genomic imprinting at a cluster of imprinting genes on the distal end of mouse Chromosome 7. At one end of the cluster are three genes that are exclusively expressed from the maternal chromosome. In the middle of the cluster are two paternally expressed genes encoding the growth factors insulin and insulin-like growth factor II (IGFII). At the far end of the cluster lies the *H19* gene, an unusual gene that codes for a non-translatable RNA whose expression is exclusively maternal.

The clustering of five imprinted genes raised the possibility that imprinting, like X chromosome inactivation, is controlled by a signal or signals which can act over large distances and multiple genes. To date there is little evidence to support this notion. However the laboratory has established a mechanistic link between the expression of *H19,Igf-2* and *Ins-2* that relies on a competition between their promoters for a set of shared enhancers. The competition is regulated by a region of extensive paternal-specific DNA methylation on the *H19*. A possible role for the *H19* gene product itself in imprinting has been excluded by the analysis of a null allele of *H19* that shows no disruption in the imprinting process.

With a growing list of imprinted genes in hand, the challenge is now to determine the function of allelic inactivation by imprinting. The function presumably must confer some selective advantage to the organism, as it must counterbalance the obvious attendant risk of hemizygosity. Several explanations have been proposed for the acquisition of genomic imprinting in eutherian mammals. To date the most compelling model has been provided by David Haig and his colleagues who suggest that imprinting evolved in mammals because of the conflicting interests of maternal and paternal genomes within a litter. In mammals, which are primarily non-monogamous, the mother provides significant maternal resources to the offspring both during intra-uterine life as well as during suckling after birth. Successful passage of paternal genes into the next generation is best ensured by having the embryos consume maternal resources, even if by so doing the fitness of her future litters is compromised. The mother's interests are best served by distributing her resources more equitably among litters. According to this model, the two

parents have silenced or imprinted different sets of growth-promoting and growth-restricting genes in order to accomplish their differing reproductive goals.