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COMMENTARY

Overview of *Mammalian Genome* special issue on epigenetics

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In 1942 C.H. Waddington devised the term "epigenetics" to describe the causal mechanisms of development from the fertilised egg to adult (Waddington 1942). In broad terms this definition still holds, but with time, and increasing knowledge, the term "epigenetics" now covers the study of heritable chromatin modifications that regulate gene expression but do not alter DNA sequence. These modifications comprise modifications of histone proteins and DNA, epigenetic marks that are heritable in mitotically dividing cells. Epigenetic marks are key to fundamental developmental processes of differentiation, X chromosome inactivation, and genomic imprinting. Aberrant epigenetic marks are associated with developmental disorders and, increasingly, with diseases that manifest in adults.

The main topics covered in this special issue of *Mammalian Genome* are genomic imprinting and the role of epigenetics in disease. However, one of the earliest epigenetic phenomena to be studied in mammals was X chromosome inactivation whereby one of the two X chromosomes in females is silenced. In this issue Shevchenko et al. describe a cytogenetic analysis of epigenetic marks on the inactive X (Xi) of the vole *Microtus rossiaemeridionalis* and found both similarities and differences when compared with the more widely studied mouse and human Xi.

Genomic imprinting

Genomic imprinting was recognised in the mid-1980s in mouse nuclear transplantation and genetic experiments (Cattanach and Kirk 1985; McGrath and Solter 1984; Surani et al. 1984). The nuclear transplantation experiments showed that parental genomes must be marked or imprinted during parental gametogenesis to function differently in the zygote, and the genetic experiments showed that it was only specific regions of certain chromosomes, implying specific genes, that were so imprinted. The first imprinted genes were discovered in 1991 (Barlow et al. 1991; DeChiara et al. 1991) and now about 100 are known in Eutherian mammals (Williamson et al. 2009). These genes are expressed according to parental origin, with expression controlled by epigenetic marks.

Imprinted genes tend to be arranged in clusters, ranging in size from less than 100 kb to over 1 Mb. Tierling et al. show that the gene *Begain* marks the proximal boundary of the cluster of imprinted genes on mouse chromosome 12, and extends the size of the cluster by 600 kb.

A master regulator, the imprinting centre, controls parental specific gene expression within a cluster. All imprinting centres are marked by differential methylation according to parental origin, and there has been considerable progress in understanding how these marks are established in the germline and subsequently maintained. More recently, differential histone modifications have been described at imprinting centres and the intimate links between DNA methylation, histone methylation, and non-histone proteins are just starting to be understood. In this issue Weaver et al. and Feil and Kacem review epigenetic changes in development associated with imprinting. However, we have limited understanding of the mechanisms whereby the methylation machinery is targeted to imprinting centres, although new data show that demethylation of histones is a necessary first step (Ciccone et al. 2009). The target for DNA methylation is CpG, a dinucleotide that tends to occur in clusters called CpG islands

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(CGI) found in imprinting centres. CGIs are defined algorithmically and Irizarry et al. describe the development of a new and improved algorithm that they used to demonstrate both evidence for CGI in all multicellular organisms that have been sequenced and a substantial loss of CpGs in animals of greater complexity. The genes *Dnmt3a* and *Dnmt3L* that establish methylation have a preference for CpGs 8–10 bp apart, but Glass et al. show that this periodicity does not fully account for the distribution of cytosine methylation.

All well-characterised imprinted clusters contain long noncoding RNA. Functional testing has shown that two, *Airn* and *Kcnq1ot1*, are required for epigenetic silencing of multiple genes within their respective clusters. The mechanism of action of these RNAs, and also of *Xist*, the long noncoding RNA essential for X chromosome inactivation, is the subject of intense study. Recent evidence indicates that all three silence genes through an interaction with chromatin. Recent progress is reviewed by Nagano and Fraser, who suggest that silencing by long noncoding RNAs is dependent on their ability to recruit histone-modifying activities to chromatin.

Imprinted genes are functionally haploid, a condition believed to be selectively disadvantageous. Das et al. review theories to account for the evolution of imprinting. One widely accepted theory is the "conflict" or "kinship" hypothesis that postulates that there are differing selective pressures on paternally and maternally derived genes (Moore and Haig 1991). Thus, it is in the interest of paternal genes in offspring to acquire resources from the mother, but it is in the interest of maternal genes to be sparing in the demand for these resources. Drake et al. present new data from studies of the imprinted gene *Rasgrf1* that provide support for the "conflict" hypothesis and suggest that *Rasgrf1* acts upstream of a major growth factor, insulin growth factor 1 (IGF1).

Epigenetics and health and disease

The early genetic experiments showed that uniparental inheritance of imprinted regions of the genome in the mouse could result in abnormal phenotypes, many of which affect growth and viability, paving the way for identification of human disorders attributable to anomalies in imprinted genes or the imprinting process. Das et al. review the role of imprinting in human disease. Evidence is accumulating for epigenetic effects in human disorders where imprinted effects are not apparent. Detailed reviews of some of these, e.g., cancer, deafness, psychiatric disorders, and type 1 diabetes, appear in this issue. Valeri et al. discuss epi-miRNAs, microRNAs that target genes involved in modifying epigenetic marks, and the contribution of these microRNAs to cancer. Conversely, they discuss the epigenetic misregulation of microRNA expression that occurs in malignancies. Friedman and Avraham consider the implications for deafness of epigenetic regulation in the inner ear. Malvaez et al. review the role of epigenetic regulation in long-term memory and in drug-induced behavioural responses. They present much evidence showing that the chromatin-modifying enzymes such as histone acetyl transferases and histone deacetylases modulate initial memory consolidation and memory extinction processes, and they propose that these enzymes have potential as therapeutic targets for both anxiety and drug abuse disorders. MacFarlane et al. postulate that epigenetic changes play a role in initiation or progression of susceptibility to type 1 diabetes via environmental factors such as diet influencing the epigenetic regulation of key genes involved in beta cell homeostasis and autoimmunity. Furthermore, diabetic physiology can alter methyl group metabolism and potentially modify epigenetic changes. French et al. examine the evidence that interindividual variation in epigenetic marks carried on histones and DNA, attributable to genomic and/or environmental effects, may also play a role in disease or disease susceptibility. A model to detect modifiers of imprinting effects is presented by Wolf and Cheverud.

Abnormal epigenetic reprogramming of imprinted genes is associated with assisted reproductive technologies in humans, but Peters et al. have been unable to confirm epigenetic effects in mouse studies.

In conclusion, the articles in this issue reflect the current knowledge of the contribution of epigenetics to imprinting and to disease. It is evident that enormous progress is being made in unraveling the complex molecular mechanisms governing the control of expression of imprinted genes. It is also evident that epigenetic alterations play a role in many human diseases, and one challenge is a better understanding of these modifications at a molecular level to enable new therapeutic interventions.

References

Barlow DP, Stoger R, Herrmann BG, Saito K, Schweifer N (1991) The mouse insulin-like growth factor type-2 receptor is imprinted and closely linked to the *Tme* locus. Nature 349:84–87

Cattanach BM, Kirk M (1985) Differential activity of maternally and paternally derived chromosome regions in mice. Nature 315:496–498

Ciccone DN, Su H, Hevi S, Gay F, Lei H et al (2009) KDM1B is a histone H3K4 demethylase required to establish maternal genomic imprints. Nature 461:415–418

DeChiara TM, Robertson EJ, Efstratiadis A (1991) Parental imprinting of the mouse insulin-like growth factor II gene. Cell 64:849–859

McGrath J, Solter D (1984) Completion of mouse embryogenesis requires both the maternal and paternal genomes. Cell 37:179–183

Moore T, Haig D (1991) Genomic imprinting in mammalian development: a parental tug-of-war. Trends Genet 7:45–49

Surani MA, Barton SC, Norris ML (1984) Development of reconstituted mouse eggs suggests imprinting of the genome during gametogenesis. Nature 308:548–550

Waddington CH (1942) The epigenotype. Endeavour 1:18–20

Williamson CM, Blake A, Thomas S, Beechey CV, Hancock J et al (2009) Mouse imprinting data and references. Available at: http://www.har.mrc.ac.uk/research/genomic_imprinting