Variable silencing of the repeat genome – implications for non-genetic inheritance

Tessa M. Bertozzi[1], Anne C. Ferguson-Smith[1]
[1]Department of Genetics, University of Cambridge, Cambridge CB2 3EH, UK

Generally repressed by epigenetic mechanisms, retrotransposons represent around 40% of the murine genome. At the *Agouti viable yellow* (A^{vy}) locus, an endogenous retrovirus (ERV) of the intracisternal A-particle (IAP) class retrotransposed upstream of the agouti coat-colour locus, providing an alternative promoter that is variably methylated in genetically identical individuals. This results in variable expressivity of coat colour that is inherited across generations. The A^{vy} mouse has been used as both a model for non-genetic inheritance and as a potential epigenetic biosensor of environmental compromise. Given how widespread ERVs are in the mouse genome, we set out to determine the prevalence of this phenomenon.

We conducted a systematic screen using whole-genome bisulfite sequencing (WGBS) datasets and identified a repertoire of variably methylated IAPs (VM-IAPs) possessing A^{vy}-like properties. Each exhibits variable methylation levels between individuals but a stable methylation state within an individual. Only in rare instances do they act as promoters controlling adjacent gene expression. Their methylation state is locus-specific within an individual and their flanking regions are enriched for CTCF. VM-IAPs are reprogrammed after fertilization and re-constructed as variable loci in the next generation. Only a single locus exhibits evidence of epigenetic inheritance and the effect size is small. Similar to A^{vy}, abnormal folate metabolism shifts VM-IAP methylation levels. Our catalogue of novel loci will prove useful in studying the mechanisms underlying repeat element silencing and reconstruction of epigenetic variability across generations, as well as in exploring the epigenetic impact of altered environmental contexts.