EPIGENETICS

Do mothers and fathers imprint differently?

For a handful of mammalian genes it matters whether it is the maternal or the paternal allele that is expressed. This parental imprinting is achieved through an epigenetic mechanism, which has been extensively studied for a few loci. New work from Shirley Tilghman's group sheds light on the mechanism that ensures maternal expression of a gene cluster on mouse chromosome 7. Importantly, these findings add to the appealing possibility that maternally and paternally imprinted genes are silenced by fundamentally different mechanisms.

Among the imprinted genes on mouse chromosome 7 is *Kcnq1*. It encodes a potassium channel and, although its early embryonic expression is exclusively maternal, it later becomes biallelic. Intron 10 of *Kcnq1* contains a promoter for a non-coding paternally expressed transcript, *Kcnq1ot1*, and it is this promoter that had previously been shown to be required for paternal silencing of

several neighbouring genes, including *Cdkn1c*, which is maternally expressed throughout life. The authors show that a small, 244-bp deletion of the promoter abolishes *Kcnq1ot1* transcription. Paternal, but not maternal, inheritance of this deletion abolished silencing of all the imprinted genes in the cluster on the paternal allele, showing that transcription of *Kcnq1ot1* is required for their imprinting.

Using homologous recombination, the authors inserted a polyA-based transcriptional stop element to significantly shorten the *Kcnq1ot1* transcript. They show that premature termination of the paternal but not the maternal allele abolished imprinting in the cluster, indicating that it is not the act of transcription but the transcript itself, or its elongation, that is necessary for imprinting in this region. The mechanism by which these non-coding RNAs silence their target genes awaits elucidation, although the authors show that the highly conserved repeats in the 5' end of *Kcnq1ot1* are dispensable for silencing.

Two imprinting mechanisms have been described to date: one involves an imprinting control region (ICR) at

the well-studied *H19/Igf2* locus. On the maternal chromosome the ICR acts as an insulator to inhibit expression of *Igf2*, whereas DNA methylation of the ICR on the paternal allele spreads to and silences the *H19* gene. The other mechanism involves an ICR that acts as a promoter for a paternally expressed non-coding RNA, first described at the *Igf2r* locus by Denise Barlow and colleagues. *Kcnq1ot1* is the second example of a non-coding RNA with a direct role in the silencing of imprinted genes. The fact that the activity of the ICR in the first mechanism occurs on the maternal chromosome whereas in the second, described by Tilghman and colleagues, the activity applies to the paternal chromosome raises the possibility that the two mechanisms are gender-specific. Understanding how other clusters of imprinted genes are silenced should verify this interesting possibility.

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ORIGINAL RESEARCH PAPER

Mancini-DiNardo, D. et al. Elongation of the *Kcnq1ot1* transcript is required for genomic imprinting of neighboring genes. *Genes Dev.* **20**, 1268–1282 (2006)

FURTHER READING Pauler, F. M. & Barlow, D. P. Imprinting mechanisms — it only takes two. *Genes Dev.* **20**, 1203–1206 (2006)

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URLs

Cdkn1c

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=12577

H19

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=14955

Igf2

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=16002

Kcnq1

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=16535

Kcnq1ot1

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=63830