Nature Reviews Genetics | AOP, published online 17 December 2013; doi:10.1038/nrg3659

Photodisc/Getty

EPIGENETICS

Reprogramming with TET

Genomic imprinting is an important mechanism in mammalian development. It results in gene expression exclusively from either the maternal or the paternal allele and is regulated by allele-specific DNA methylation. During reprogramming of primordial germ cells (PGCs, which are precursors of the germline), these methylation marks are erased in order to wipe the slate clean for establishment of the relevant imprinting pattern in the next generation. The enzymes involved have been elusive, but Yamaguchi *et al.* have now found a role for methylcytosine dioxygenase TET1 in this process.

TET1 is expressed in PGCs and is a member of the ten-eleven translocation (TET) family of proteins that oxidize 5-methylcytosine. The authors investigated a potential role for TET1 in reprogramming PGCs by generating mice from fathers in which *Tet1* had been knocked out. They hypothesized that the germline of the fathers would have aberrant imprinting erasure and the offspring of these mice would thus be developmentally affected. Indeed, phenotypic effects on the next generation included early embryonic lethality, placental and growth defects, and postnatal growth retardation.

The authors noted a similarity between the phenotypic effects of the paternal *Tet1* knockout and those of the knockout of paternally expressed 10 (*Peg10*), which is an imprinted gene, and therefore hypothesized that the paternal knockout resulted in a loss of imprinting at *Peg10*. An RNA sequencing analysis revealed deregulated expression of *Peg10*, as well as 11–46 of 80 imprinted genes that normally show expression from the paternal allele. In each case, the maternally expressed genes were upregulated and the paternally expressed genes were downregulated, which indicated a 'maternalization' of imprinted genes. The hypothesis that this was because the imprinted genes had increased methylation at the paternal allele was confirmed by bisulphite sequencing. Furthermore, a specific analysis of the placenta indicated that this maternalization was probably responsible for the placental defects, as imprinting deregulation occurred in the relevant genes.

To probe whether the hypermethylation seen at imprinted genes in the embryos and the placentas was a result of germline defects, the authors analysed the methylation patterns of both PGCs and sperms in the *Tet1*-knockout males by reduced representation bisulphite sequencing. The results showed that most of the embryonic and placental hypermethylation can be traced back to the sperms and the PGCs. Furthermore, a time-course analysis of these cells indicated that TET1 is important in the second wave of demethylation in PGCs, in which it targets a specific set of genes. Hence, this explains why only few imprinted genes were affected by knocking out *Tet1*.

Using maternal *Tet1* knockouts, the authors then showed that TET1 also plays a part in maternal genomic imprinting; thus, TET1 has an important role in genomic imprinting erasure in PGCs of both sexes. The next step will be to investigate its potential role in humans and whether its deregulation is the cause of developmental defects.

Hannah Stower

ORIGINAL RESEARCH PAPER Yamaguchi, S. *et al.* Role of Tet1 in erasure of genomic imprinting. *Nature* http://dx.doi.org/10.1038/nature12805 (2013)