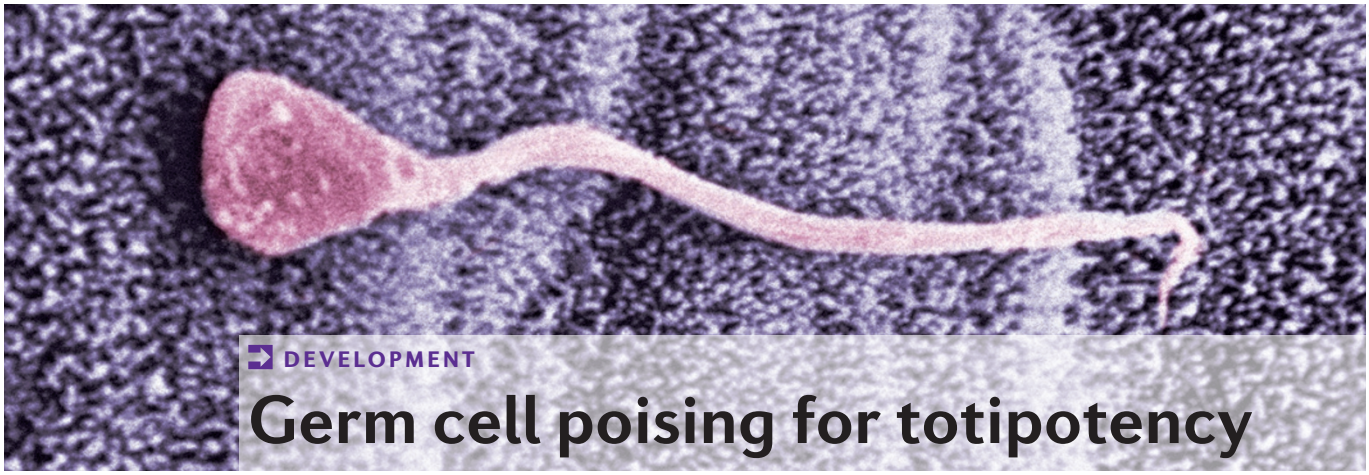
Nature Reviews Genetics | AOP, published online 1 October 2013; doi:10.1038/nrg3596



ImageSource/NPG

DEVELOPMENT

Germ cell poising for totipotency

> … poised genes are heavily enriched for key regulators of the differentiation of many different tissue types

Mammalian eggs and sperm are highly specialized, differentiated cells, but when they fuse at fertilization the resulting zygote is able to give rise to an entire individual and its extraembryonic tissues. How this totipotency of the zygote is restored from differentiated gametes remains a fundamental question in developmental biology. A new study in the mouse now provides evidence that epigenetic poising of key developmental genes in germ cells — both the maturing gametes and their precursors — has a crucial role.

In embryonic stem (ES) cells the promoters of a set of important developmental regulatory genes are characterized by their bivalent chromatin state; that is, both the 'activating' modification histone 3 lysine 4 trimethylation (H3K4me3) and the 'repressive' modification H3K27me3 are found at their promoters. This bivalency keeps genes poised for rapid activation or repression — a feature that is thought to be important for pluripotency. It has been hypothesized that similar poising might underlie the ability of gametes to confer totipotency on the zygote, and it is this question that Lesch and colleagues set out to investigate.

The authors isolated germ cells from male and female mouse embryos at days 12.5 (E12.5), 13.5 and 14.5 of development using flow cytometry. To profile chromatin in these cells, they adapted recently developed protocols for carrying out chromatin immunoprecipitation followed by sequencing (ChIP–seq) in small numbers of cells. First, considering both sexes and all three developmental times together, the authors identified a set of genes that have the features of bivalent chromatin — high levels of both H3K4me3 and H3K27me3. Expression profiling by RNA sequencing (RNA–seq) showed that the genes in this set also have low expression levels at each developmental stage.

These findings provide an indication that, similar to ES cells, epigenetic poising occurs in germ cells. However, germ cells go through several stages during which large-scale epigenetic changes occur, so the authors investigated whether any of these genes retain the hallmarks of poising through these transitions. To do this, they identified specific promoters that met quantitative criteria for the poised state (using H3K4me3, H3K27me3 and expression status) and examined male and female germ cells separately. This analysis revealed a set of 147 genes that are poised from E12.5 to E14.5 in germ cells from both sexes, and the authors also provide evidence that a substantial proportion of these genes are poised from at least E11.5. These poised genes are heavily enriched for key regulators of the differentiation of many different tissue types.

Finally, the authors examined whether poising is maintained following meiosis in maturing gametes, although it was only possible to address this question in male gametes because of the difficulty in obtaining sufficient numbers of oocytes. This analysis identified 92 poised genes that overlap with the 147 genes in which poising is maintained throughout earlier stages, supporting a germ cell poising theory of totipotency re-establishment in the zygote.

Although ultimate support for this theory will lie in determining whether poising persists at fertilization and beyond, this study provides a compelling explanation of how the potential to form a new individual can be maintained through the whole developmental cycle of the germ line.

Louisa Flintoft

ORIGINAL RESEARCH PAPER Lesch, B. J. *et al.* A set of genes critical to development is epigenetically poised in mouse germ cells from fetal stages through completion of meiosis. *Proc. Natl Acad. Sci. USA* http://dx.doi.org/10.1073/pnas.1315204110 (2013)