Researchers uncover two reprogramming stages in the development of gametes

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(Phys.org)—A research team from the University of California has identified two reprogramming events that occur during the development of oocytes and sperm leading to the formation of gametes in humans. In studying aborted human fetuses, the researchers, as they describe in their paper published in the journal *Nature Cell Biology*, found they were able to isolate oocytes and sperm and then to follow their development into gametes.

This new research is part of an effort to understand why approximately 10 percent of people are born infertile. Scientists believe that it's possibly due to problems that occur during the very earliest stages of fetal development. In the first few weeks after conception – after oocytes in females and sperm in males appear – the development of balls of cells known as gametes come about. Up till now, most research focusing on the development of gametes has been done on mice, however, due to the sensitivity of studying actual human early fetal development – to do so generally means the destruction of the fetus. In this new research, the team from California received permission to use samples of aborted fetuses from the University of Washington's Birth Defects Research Laboratory.

By studying fetal samples taken at different stages of development (from 6 to 20 weeks) the team was able to piece together the developmental process that leads to the fully developed gamete. In looking at the developmental process the team discovered two distinctive events occurring – one before six weeks, and the other after. Both involved

reprogramming epigenetic modifications – changes to the structure of DNA molecules that have an impact on how genes in them are expressed. This finding doesn't explain why some people are born infertile, of course, but it does provide a road map of sorts that researchers can use to trace the development of the cells that are responsible for reproduction later in life.

Also, in comparing 6 week old germ cells that had been raised in their lab with those grown naturally inside the womb, they found that the two didn't match, suggesting that a process occurs in utero causing the germ cells to change, that is still not understood.

More information: The ontogeny of cKIT+ human primordial germ cells proves to be a resource for human germ line reprogramming, imprint erasure and in vitro differentiation, *Nature Cell Biology*, (2012) doi:10.1038/ncb2638

Abstract
The generation of research-quality, clinically relevant cell types in vitro from human pluripotent stem cells requires a detailed understanding of the equivalent human cell types. Here we analysed 134 human embryonic and fetal samples from 6 to 20 developmental weeks and identified the stages at which cKIT+ primordial germ cells (PGCs), the precursors of gametes, undergo whole-genome epigenetic reprogramming with global depletion of 5mC, H3K27me3 and H2A.Z, and the time at which imprint erasure is initiated and 5hmC is present. Using five alternative in vitro differentiation strategies combined with single-cell microfluidic analysis and a bona fide human cKIT+ PGC signature, we show the stage of cKIT+ PGC formation in the first 16 days of differentiation. Taken together, our study creates a resource of human germ line ontogeny that is essential for future studies aimed at in vitro differentiation and unveiling the mechanisms necessary to pass human DNA from one generation to the next.