




# The Non-equivalence of Mammalian Pronuclei

It is generally assumed that males and females carry equivalent haploid genomes. Indeed, one of the fundamental tenets of Mendelian genetics is that genes derived from the sperm are functionally equivalent to those derived from the egg. However, as we saw in Chapter 2, genomic imprinting can occur in mammals such that the sperm-derived genome and the egg-derived genome may be functionally different and play complementary roles during certain stages of development. Genomic imprinting is thought to be caused by the different patterns of cytosine methylation.

The first evidence for nonequivalence came from studies of a human tumor called a hydatidiform mole, which resembles placental tissue. A majority of such moles have been shown to arise when a haploid sperm fertilizes an egg in which the female pronucleus is absent. After entering the egg, the sperm chromosomes duplicate themselves, thereby restoring the diploid chromosome number. However, the entire genome is derived from the sperm (Jacobs et al. 1980; Ohama et al. 1981). The cells survive, divide, and have a normal chromosome number, but development is abnormal. Instead of forming an embryo, the egg becomes a mass of placenta-like cells.

Normal development does not occur when the entire genome comes from the male parent. Normal mammalian development also does not occur when the genome is derived totally from the egg.\* Placing mouse oocytes in a culture medium that artificially activates the oocyte while suppressing the formation of the second polar body produces diploid mouse eggs whose genes are derived exclusively from the oocyte (Kaufman et al. 1977). These eggs divide to form embryos with spinal cords, muscles, skeletons, and organs, including beating hearts. However, development does not continue, and by day 10 or 11 (halfway through the mouse's gestation), these parthenogenetic embryos deteriorate. Neither human nor mouse development can be completed solely with egg-derived chromosomes.

That male and female pronuclei are both needed for normal development was also shown by pronuclear transplantation experiments (Surani and Barton 1983; McGrath and Solter 1984; Surani et al. 1986). Either male or female pronuclei can be removed from recently fertilized mouse eggs and added to other recently fertilized eggs. (The two pronuclei can be distinguished at this stage because the female pronucleus is the one beneath the polar bodies.) Thus, zygotes with two male or two female pronuclei can be constructed. Although these eggs will form diploid cells that undergo normal cleavage, eggs whose genes are derived solely from sperm nuclei or solely from oocyte nuclei do not develop to birth. Control eggs undergoing such transplantation (i.e., eggs containing one male and one female pronucleus taken from different zygotes) can develop normally (Table 1). Thus, for mammalian development to occur, both the sperm-derived and the egg-derived pronuclei are critical.

Class of reconstructed zygotes	Operation	Number of successful transplants	Number of surviving progeny
Bimaternal		339	0
Bipaternal		328	0
Control		348	18

Source: McGrath and Solter 1984.

Table 1 Pronuclear transplantation experiments

The reason for the necessity of having both sperm-derived and egg-derived genomes is that there are approximately 100 mammalian genes that are expressed only from the sperm-derived chromosomes or only from the egg-derived chromosomes. Such genes are called imprinted genes. For example, the human *DLK1* gene, encoding a signaling protein that inhibits fat cell formation, is only expressed from the sperm-derived chromosome 14. The *UBE3A* gene on chromosome 15 is only expressed from the maternally derived chromosome, where its protein product will help regulate brain cell mitoses (Singhmar and Kumar 2011). Thus a *UBE3A* mutation on the maternal chromosome cannot be compensated for by a wild-type allele on the paternal chromosome. The regulator of these transcriptional differences is DNA methylation. Differentially methylated regions (DMRs) are found near genes that regulate transcription. The DMRs for maternal-specific methylation (i.e., gene expression from the paternal copy) are usually located at promoters of these genes, whereas the DMRs for paternal-specific methylation (i.e., gene expression from the maternal copy) are usually located in intergenic regions (such as that controlling the CTCF-dependent insulator element discussed in Chapter 2). These methylation patterns are erased during germ cell migration and established during gametogenesis (see Bartolomei and Ferguson-Smith 2011).

The importance of DNA methylation in this block to parthenogenesis was demonstrated when Kono and colleagues (2004) generated a female mouse whose genes came exclusively from two oocytes. To accomplish this feat, they had to mutate the DNA methylation system in one of the oocyte genomes to make it more like that of a male mouse, and then they had to perform two rounds of nuclear transfer. “Men,” as one reviewer remarked, “do not need to fear becoming redundant any time soon” (Vogel 2004).

\*The eggs of many invertebrates and some vertebrates are capable of producing a normal embryo in the absence of any spermatid contribution, an ability known as *parthenogenesis* (Greek, “virgin birth”). Mammals, however, do not exhibit parthenogenesis.

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