<Further Development 13_03>

Epigenetic Regulation of Histone States Is Required for the Maternal to Zygotic Transition in the Mouse

Transcriptional "awakening" of the mouse zygotic genome occurs in two waves--a minor activation of some genes during fertilization and a major Zygotic Gene Activation (ZGA) event in the two cell embryo. Transcription from the zygotic nuclei is critical in passing beyond the 2-cell stage (Abe et al 2018).

In attempting to find the protein(s) responsible for the mammalian ZGA, Gassler and colleagues (2022) looked for similar regulatory sequences in 985 genes that appeared to be upregulated at that time. They found that a particular sequence-- TCAAGGCCA--was present in a high proportion of these genes, and that this was the binding site for the **Nr5a2 pioneer transcription factor**. This protein is known to be important later in development to retain the pluripotency of the inner cell mass blastomeres; but its function in ZGA had not been appreciated. Gassler and colleagues found that Nr5a2 was present in 2-cell embryos and that its transcript was already present in the oocyte and zygote. If Nr5a2 was experimentally removed from the zygotes, they could not divide well and died. Nr5a2 inhibition resulted in down-regulation of 5891 genes, including 72% of genes expressed at ZGA. Nr5a2 binds to near the initiation sites of these genes, where it binds to nucleosomes and directly promotes chromatin accessibility.

In order for the zygotic genes to be activated, the parental chromatin undergoes many changes. New histones are placed on the DNA during the early cell divisions, and the gamete-specific DNA methyl groups are removed (except for those on imprinted genes). In both mice and human embryos, the DNA methylation of sperm and egg chromatin is almost entirely removed. While some “imprinted gene” methylation remains, that which is concerned with cell differentiation appears to be removed. This allows an almost “clean slate” for the newly forming blastocyst cells. New DNA methylation patterns characteristic of totipotent and pluripotent cells are established (Abdalla et al. 2009; Guo et al. 2014; Smith et al. 2014). Thus, by the 16-cell stage, the genome of each cell is hypomethylated and each of these 16 cells appears to be pluripotent (Tarkowski et al. 2010). The stage is now set for cell differentiation to take place.

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