Research

Developmental Epigenetics & Disease

Functional specialization of cells during development is the outcome of their differential transcriptional programs. These programs are driven by the transcription/translation machinery, which in turn is guided and controlled by epigenetic modifications of both DNA and chromatin. This epigenome, which does not affect the genetic code itself, is robust and heritable at each mitotic cell division, yet remarkably adaptable under circumstances of differentiation and cell fate commitment. Unquestionably, the epigenome is most flexible during germ cell formation, the oocyte-to-embryo transition (OET) and very early embryonic development, when epigenetic reprogramming must take place to create the unique environment producing the totipotent state.

During this transition, nuclear reprogramming resets the epigenome of both parental pronuclei to a ground state. Radical, global DNA demethylation, occurring actively in the paternal and passively in the maternal genome is a prominent feature of nuclear reprogramming, yet this process poses a danger to a subset of methylated sequences that must be preserved for their germ-line to soma inheritance. Prominently, imprinted loci, gene clusters with parent-of-origin specific gene expression patterns, must retain their differential methylation status acquired during gametogenesis throughout embryogenesis and in adult tissues.

We have identified a complex, formed by maternal TRIM28/KAP1 and its binding partners ZFP57 and SETDB1, playing an essential role preventing detrimental demethylation of imprinted genes during reprogramming. The loss of maternal TRIM28 leads to severe phenotypic and epigenetic variability ultimately resulting in embryonic lethality. Though usually attributed to genetic background variations or environmental influence, we show the phenotypic variability to be derived from early and minute epigenetic variations in single blastomeres. The, at best, partial rescue by paternally expressed TRIM28 is owed to the methylation-dependent DNA binding of the complex. A full rescue of all developmental defects can however be achieved by mere pronuclear transfer of maternal mutant pronuclei into normal enucleated zygotes, thus timing the requirement of maternal TRIM28 protein to the zygote shortly after fertilization, proving it expendable for oocyte growth and maturation. Our results not only shed light on the long elusive players protecting imprinting marks in the shifting epigenetic environment of the early preimplantation embryo, but also reveal the long-ranging effects of a maternal gene deletion on epigenetic memory and illustrate the delicate timing and equilibrium of maternal and zygotic factors during nuclear reprogramming.

Our Team