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In the Spotlight

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Imprinting Disruption by Mutant *Trim28* Leads to Embryo Lethality

Genomic imprinting, the process by which gene expression is determined to arise from the maternal or paternal chromosome, is based on differential epigenetic modifications that are greatly dependent on differently methylated regions (DMRs) at specific loci. Disruptions on the methylated patterns of these imprinted loci are known to be associated with severe genetic disorders and multiple cancers.

During early embryo formation, protection of the germ line methylated imprinted loci is crucial, as the transition from oocyte to embryo is associated with extensive gamete epigenetic reprogramming that involves partial demethylation of the paternal genome. Therefore, maternal genome protection during a time of active demethylation is dependent on several proteins and factors that prevent it from occurring at specific DMRs.

The relevance of these protective proteins on the maintenance of proper imprinting during embryo development has recently been reinforced after a report by Messerschmidt et al in *Science* (*Science*. 335:1499-1502), where the researchers demonstrate that embryonic lethality results from the misregulation of genomic imprinting in mice lacking maternal tripartite motif–containing 28 (*Trim28*).

Trim28, also known as Krüppel-associated protein 1 (KAP1) or transcriptional intermediary factor 1β (TIF1β),encodes a central component of an epigenetic-modifier complex that recruits chromatin modification and remodeling factors, which are associated with the formation of repressive chromatin.

Messerschmidt and colleagues show that loss of maternal *Trim28* alone results in a highly pleiotropic phenotype, with 100% lethality before birth despite normal embryonic development to the blastocyst stage.

Through microarray analysis, Messerschmidt et al demonstrate that several imprinted genes are abnormally up- or downregulated in the embryonic mutants, which also present abnormal methylation patterns, as shown by pyrosequencing. The authors also show using immunoprecipitation that *TRIM28* normally binds to the DMRs with abnormal methylation and expression patterns.

Messerschmidt et al attribute the multitude of phenotypes observed in the mutant embryos to a protective role by other proteins that are able to partially ensure the maintenance of some genomic imprints and also to a random combination of stochastically affected TRIM28 target loci, due to a slow and inefficient demethylation process. This combination leads to a variable degree of mosaicism and extent of gene dysregulation that ultimately determines the time and mode of embryonic and fetal lethality.

Altogether, the findings presented by Messerschmidt and colleagues illustrate the long-range effects of a maternal gene deletion on epigenetic memory. In addition, they also particularly indicate that *Trim28* may be a potential target to explore in human cases of unexplained pregnancy loss.

The MARF1 and Female Infertility

Oocyte competency is crucial in order to achieve a normal fertilization that will ultimately lead to a successful pregnancy. This competency includes accurate completion of meiosis, proper cytoplasmic maturation, and maintenance of genomic and epigenetic integrity. All these processes rely on tightly controlled molecular signaling mechanisms to avoid abnormalities that would result in infertility, miscarriage, and/or birth defects.

Therefore, identification of all the players involved in these signaling processes is key to better understand and prevent any of the above mentioned undesirable outcomes.

Interestingly, in a recent issue of the journal *Science* (*Science*. 335:1496-1499), Su et al report the identification of mammalian ADP-ribosylation factor 1 (MARF1) as a regulatory protein to all the essential processes of mammalian oogenic competency.

The authors report that mutations in *Marf1* cause mice female infertility characterized by upregulation of a cohort of transcripts that lead to increased retrotransposon expression, defective cytoplasmic maturation, and meiotic arrest at the germinal vesicle stage.

Su and colleagues observe that the mutant *Marf1*-driven upregulation of the protein phosphatase 2 catalytic subunit (PPP2CB) is responsible for the meiotic arrest phenotype. When the mutant oocytes were induced to mature to metaphase II, there was no cleavage or embryonic development, which suggests that *Marf1* is also important for acquisition of competence to undergo fertilization and embryogenesis. In addition, the authors show that the upregulation of the Iap and Line 1 retrotransposon messenger RNAs is directly correlated with an increase in the DNA double-strand breaks in the mutant oocytes.

Thus, the findings presented by Su et al demonstrate that MARF1, by suppressing levels of specific transcripts, plays a pivotal role in establishing the network of pathways to ensure the development of a competent egg. Furthermore, they suggest that *Marf1* mutations may be on the basis of clinically unexplained cases of failed oogenic competency.