LINE-1 ACTIVITY TO EXPLAIN EARLY SPONTANEOUS MISCARRIAGE?

A well-known genetic cause of recurrent pregnancy loss is the presence of a balanced chromosomal rearrangement, as identified by karyotyping in about 4% of couples tested. More recently, exome sequencing has enabled the identification of causal embryonic lethal genes. A novel hypothesis to explain early spontaneous miscarriage has been proposed by Lou, Goodier and Qiang, Dept. of Genetics, Northwest Women's and Children's Hospital, Xi'an, China (BMC-Reproductive Health). LINE-1 retroelements are the most active autonomous transposable elements in mammals, including humans. Novel copies are generated when a LINE-1 RNA integrates into the genome by target-primed reverse transcription. About 5% of newborns have such a novel insertion, which can lead to inactivation of genes associated with hereditary disease. In addition, recombination between LINE-1 elements can generate deletions, duplications and rearrangements, and any novel insertion introduces splice sites, promoters, poly-adenylation signals and transcription factor binding sites.

The hypothesis of Lou et al. is based on the observation that, in both mouse and humans, the cellular environment of early embryonic cells is less restrictive to LINE-1 transposition. This may be associated with the successive waves of demethylation in the early embryo, as methylation of the LINE-1 promoter is inversely correlated to LINE-1 expression.
One way this hypothesis can be tested is by measuring LINE-1 methylation status and levels of LINE-1 derived nucleic acids and proteins in miscarriage samples. Possibly, an elevated LINE-1 insertion rate causes embryonic lethality by inactivation of essential genes. In addition, an accumulation of unintegrated LINE-1 DNAs that try to integrate into the genome may cause multiple genomic lesions and distract regulatory factors necessary for normal cellular processes.