Analysis of Placental Steroidogenesis as a Cause of Recurrent Miscarriage

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Background

- Recurrent miscarriage (RM) is a condition, traditionally defined as the loss of three or more consecutive clinically recognised pregnancies before 20 weeks of gestation
- RM affects 1-3% of couples trying to conceive; factors such as uterine abnormalities, maternal hypothyroidism and parental balanced translocations are associated with this condition
- In approximately 40-50% of these couples, the underlying causes are currently unexplained, but many do go on to have successful pregnancies
- These conditions have a huge psychological and clinical impact on families and couples trying to conceive, especially as the underlying cause is often unknown
- The coexistence of RM and live births in many families suggests a potential association with an underlying recessive, X-linked or imprinted condition
- The main steroid needed to maintain pregnancy is progesterone (P₄). In humans, progesterone synthesis occurs from the maternal corpus luteum in the first 6-8 weeks of gestation at which point the fertilally-derived placenta takes over progesterone production ("luteal-placental shift")
- The progesterone receptor (PGR) is the only classic ligand nuclear receptor without an associated disorder in humans

Hypothesis

Are There Genetic Mechanisms Disrupting Placental Steroidogenesis That Cause Recurrent Miscarriage?
- Progesterone is a key hormone involved in the maintenance of pregnancy. We hypothesise that defects in progesterone pathway could be a cause of RM where the current aetiology is unknown

Methods

Targeted Sequencing of RM Cohorts and Placental Single Cell Data
- A custom targeted array capture (Agilent HaloPlex) was designed that included up to 257 genes potentially involved in placental steroidogenesis, growth and fetal survival
- Capture libraries were prepared from the following cohorts and under went next generation sequencing (Illumina NextSeq)
- Using online placental single cell RNA-sequencing (scRNA-seq) data repositories, we short-listed genes expressed in the placenta (in particular, the syncytiotrophoblast cluster) and genes involved in placental steroidogenesis for analysis

Results

Placental Single Cell Data
- Our review of data focused on genes involved in placental steroidogenesis; in particular, the progesterone (P₄) synthesis pathway
- Key P₄ pathway genes were found to be localised to a cell cluster in the syncytiotrophoblast
- The progesterone receptor (PGR) was localised to the maternal decidua, as expected

Targeted Sequencing of Couples With Recurrent Miscarriage
- Targeted sequencing data from 110 couples with a history of recurrent miscarriage were analysed for mutations shared between partners at variant level, focusing on rare variants ranging from 20% to 0.5% Minor Allele Frequency (MAF) within key P₄ pathway genes
- No likely pathogenic variants were found in key members of the P₄ synthesis pathway

Summary

- The luteal-placental shift is a key event in progesterone synthesis and the maintenance of pregnancy past the first trimester
- Defects in core components of placental progesterone production are not likely to be common causes of pregnancy loss in couples with a history of recurrent miscarriage

References:
[4] References: North East Thames Regional Genetics Laboratory © The Authors