Editorial

Telomere & Early Senescence Trophoblast in Preeclampsia: Impact & Opportunity

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In general, and with numerous studies, telomeres in trophoblast cells tend to be significantly shorter in preeclampsia compared to normal pregnancies. This telomere shortening occurs due to high oxidative stress and premature cellular senescence in the placenta.

What are Telomeres? Telomeres are the final sections of chromosomes, consisting of repeating DNA strands. Telomeres function as protective "caps" that maintain the stability of DNA and chromosomes, preventing them from being easily damaged or broken apart during cell division. Each time a cell divides, the telomeres shorten slightly. If the telomeres become too short, the cell will no longer be able to divide and will decease. This is a key indicator of biological aging.

The following details the condition of trophoblast telomeres in preeclampsia: Telomere shortening occurs due to excessive oxidative stress that triggers generalized or complete DNA damage in the placenta, causing trophoblast cells to experience premature aging. This results in cells losing the ability to physiologically maintain their telomere length. Telomeres in each DNA molecule are maintained or preserved by an enzyme called telomerase. Under conditions of high oxidative stress, this enzyme tends to decrease production or have lower levels than in normal trophoblast cells, resulting in accelerated shortening. Research shows that telomerase levels tend to be lower in preeclampsia. This telomere shortening directly contributes to placental dysfunction. The primary impact of placental dysfunction is a decreased and suboptimal ability of trophoblast cells to invade maternal blood vessels.

Is Early Onset Preeclampsia (EOP) Shorter Than Late Onset Preeclampsia (LOP)?

Type EOP refers to the premature failure of uterine spiral artery remodeling in early pregnancy. This results in chronic oxygen deprivation of the placenta, which triggers an oxidative stress storm that aggressively damages the DNA strands of trophoblast telomeres. The factors that result from placental damage are known as placental site or fetal site damage. The primary trigger for premature placental failure and severe placental ischemia, leading to earlier and more severe symptoms.

In LOP, placental trophoblast cells generally form normally, and trophoblast invasion occurs normally from early pregnancy. Telomere shortening occurs late in pregnancy because the placenta essentially becomes exhausted from meeting the growing fetus's needs. Therefore, if there are other maternal comorbidities, such as obesity, hypertension, and others, this exhaustion will worsen. This is also known as a high-risk maternal or maternal site factor. The accumulation of damage is accompanied by slower and more gradual telomere shortening.

The relationship between short telomeres and implantation failure and early trophoblast invasion failure in LOP is causal and circular. This means that this cause and effect cycle repeats itself, ultimately leading to increasingly severe damage. This condition results in the phenomenon of premature placental aging. Broadly speaking, telomere shortening that is too

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rapid impairs the ability of trophoblast cells to migrate and attach to the mother's uterus. This condition trigger to failure prospective implantation in the early first trimester.

This abnormal molecular mechanism goes through the following stages: Cytotrophoblast cells, in particular, act as progenitor cells that must continue dividing for the placenta to develop. When trophoblast telomeres shorten excessively during early pregnancy, they lose chromosomal stability. This triggers a DNA damage response that forces the cells to stop dividing before the placenta is properly formed.

For implantation to proceed successfully and invade the uterine wall, trophoblast cells must differentiate into extravillous trophoblasts (EVT). The role of EVT cells is to invade the trophoblast and initiate changes in the spiral arteries known as remodeling. If telomeres shorten excessively, the differentiation program into extravillous trophoblasts is halted, resulting in a reduction in the number of differentiated cells and a slowdown in trophoblast invasion.

Short telomeres force trophoblast cells to enter cellular senescence prematurely, triggering premature cell death. These aging trophoblast cells undergo changes in secretory function (Senescence-Associated Secretory Phenotype (SASP). They release excessive amounts of pro-inflammatory cytokines and anti-angiogenic factors (such as sFlt-1).

Chronic Placental Hypoxia

Failure to invade the trophoblast, resulting in decreased spiral artery remodeling, severely restricts fetal blood flow. This condition triggers chronic hypoxia and high oxidative stress in the placenta. High levels of oxidative stress affect DNA and accelerate the shortening of remaining trophoblast telomeres. This progressively worsens placental damage, triggering clinical manifestations before 34 weeks of gestation. This occurs in the EOP type. Therefore, telomere shortening is not simply a consequence of preeclampsia but rather an early contributing factor, or upstream driver, that leads to trophoblast dysfunction during the peri-implantation period.

The Potential Use of Telomeres for Early Preeclampsia Screening

The use of telomeres for early preeclampsia screening is a cutting-edge innovation in maternal-fetal medicine. This method exploits the fact that trophoblast telomere shortening occurs at the molecular level in the first trimester, long before clinical symptoms such as hypertension appear. Placental trophoblast cells undergoing apoptosis or lysis release fragments of their genetic material into the maternal circulation. These fragments released into the maternal blood are known as free-cell DNA. This utilization is widely recognized for non-invasive screening of chromosomal and gene abnormalities, as part of non-invasive prenatal testing (NIPT). Screening is performed simply by taking a maternal blood sample (maternal blood sampling) at an early gestational age of less than 13 weeks. With a specific qPCR method, telomeres can be measured in DNA fragments derived from trophoblasts. Comparisons are needed, particularly regarding telomere length, between normal pregnancies and those at risk for developing EOP. The potential for EOP is identified when telomere length tends to be shorter than that of normal trophoblast cells at the same gestational age.

Advantages Over Conventional Biomarkers

Currently, the gold standard for early preeclampsia screening relies on the serum angiogenic ratio (such as sFlt-1/PlGF) and maternal Mean Arterial Pressure (MAP). Telomere length assessment offers a new dimension of accuracy. The sFlt-1/PlGF ratio detects the effects of endothelial dysfunction (downstream), while telomere length detects cellular senescence and biological failure of the trophoblast early in implantation (upstream). Therefore, it has high sensitivity for screening high-risk groups for EOP, which is clinically most dangerous for both mother and fetus. If first-trimester screening results show significant trophoblast telomere shortening, physicians can initiate prophylactic therapy early (before week 16), such as administering antithrombotics like low-dose aspirin to improve placentation, along with close monitoring of uterine hemodynamics.

References

1. Sultana, Z.; Maiti, K.; Dedman, L.; Smith, R. Is There a Role for Placental Senescence in the Genesis of Obstetric Complications and Fetal Growth Restriction?.2018.Am. J. Obstet. Gynecol., 218, S762–S773.
2. Maiti, K.; Sultana, Z.; Aitken, R.J.; Morris, J.; Park, F.; Andrew, B.; Riley, S.C.; Smith, R. Evidence That Fetal Death Is Associated with Placental Aging.2017.Am. J. Obstet. Gynecol., 217, 441.e1–441.e14.
3. Paules, C.; Dantas, A.P.; Miranda, J.; Crovetto, F.; Eixarch, E.; Rodriguez-Sureda, V.; Dominguez, C.; Casu, G.; Rovira, C.; Nadal, A.; et al. Premature Placental Aging in Term Small-for-Gestational-Age and Growth-Restricted Fetuses.2019.Ultrasound Obstet. Gynecol., 53, 615–622.
4. Burton, D.G.A. Cellular Senescence, Ageing and Disease. 2009.AGE, 31, 1–9.
5. Fedarko, N.S. The Biology of Aging and Frailty. 2011.Clin. Geriatr. Med., 27, 27–37.
6. Horvath, S. DNA methylation age of human tissues and cell types. 2013.Genome. Biol., 14, 3156.
7. Sultana, Z.; Maiti, K.; Aitken, J.; Morris, J.; Dedman, L.; Smith, R. Oxidative Stress, Placental Ageing-Related Pathologies and Adverse Pregnancy Outcomes.2017.Am. J. Reprod. Immunol., 77.
8. Roos, W.P.; Kaina, B. DNA Damage-Induced Cell Death by Apoptosis. 2006.Trends Mol. Med., 12, 440–450.
9. van Deursen, J.M. The Role of Senescent Cells in Ageing. 2014.Nature, 509, 439–446.
10. Campisi, J.; d'Adda di Fagagna, F. Cellular Senescence: When Bad Things Happen to Good Cells. 2007.Nat. Rev. Mol. Cell Biol., 8, 729–740.
11. Biron-Shental, T.; Sukenik-Halevy, R.; Sharon, Y.; Goldberg-Bittman, L.; Kidron, D.; Fejgin, M.D.; Amiel, A. Short Telomeres May Play a Role in Placental Dysfunction in Preeclampsia and Intrauterine Growth Restriction. 2010.Am. J. Obstet. Gynecol.202.