New insight into a placental gene pathway and its association with vitamin D

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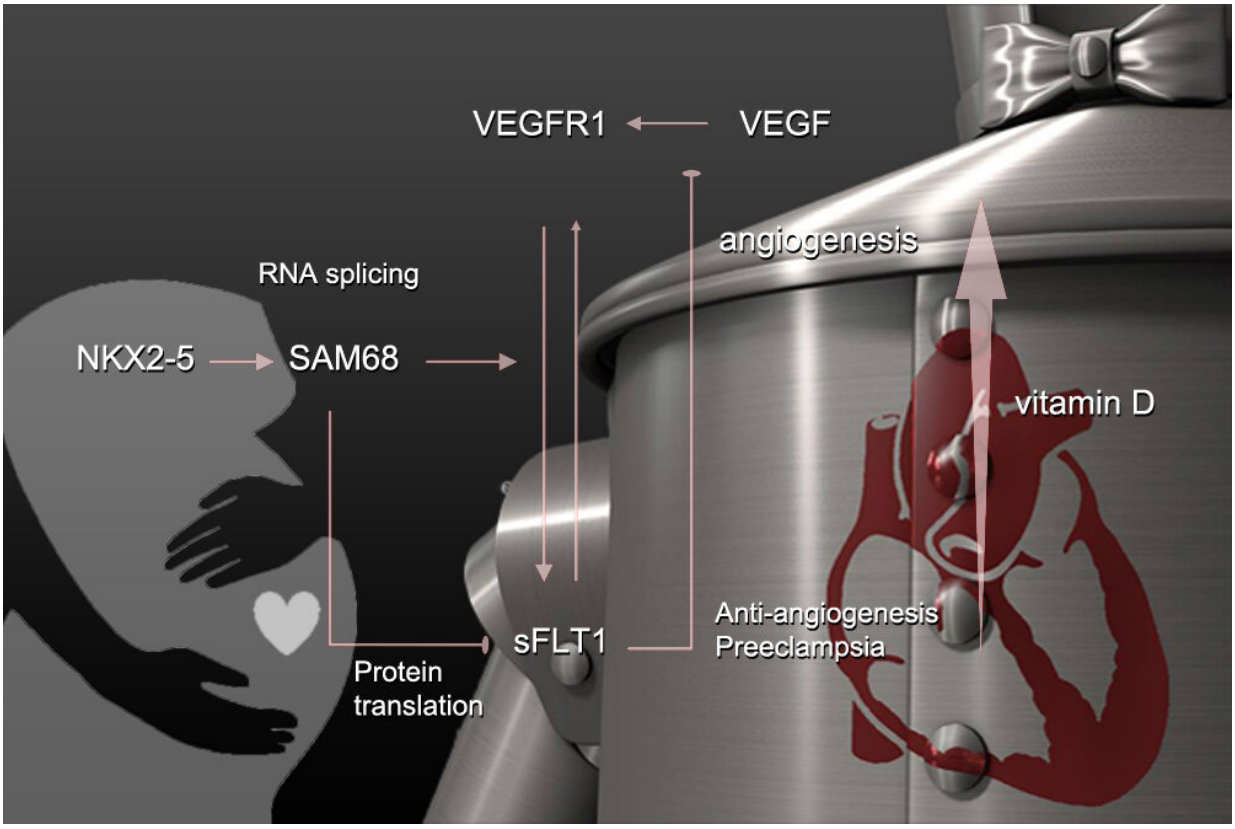

Illustration showing the relationship between preeclampsia and an axis of genes that includes NKX2-5, also known as the tinman gene. Angiogenesis is the development of new blood vessels. VEGFR1 = vascular endothelial growth factor receptor 1. Credit: MUSC

According to the World Health Organization, preeclampsia affects

between 2% to 8% of pregnancies. It can cause serious, sometimes fatal, complications in the mother and child. Among other risk factors, such as obesity and diabetes, vitamin D deficiency during pregnancy has been associated with an increased risk of preeclampsia.

In an article in *Pregnancy Hypertension*, a team of researchers at the Medical University of South Carolina (MUSC) found that expression of a set of genes previously studied in the setting of early onset and severe preeclampsia is significantly affected by vitamin D status during late-stage pregnancy.

Exactly how preeclampsia develops is unclear. Recent evidence points to poor development of blood vessels in the placenta—the organ that nourishes the fetus throughout pregnancy. This leads to hypertension and several other complications in the mother. The only cure for preeclampsia is to deliver the fetus, which can be dangerous if done too early.

In a previous study that was supported by pilot funding from the South Carolina Clinical & Translational Research Institute (SCTR), the research team led by Kyu-Ho Lee, M.D., Ph.D., assistant professor in the departments of Pediatrics and Obstetrics and Gynecology at MUSC found that the expression of three genes—NKX2-5, SAM68, and sFLT1—are highly correlated in the setting of early-onset and severe preeclampsia (EOSPE), with sFLT1 being an identified marker for preeclampsia risk. In the current study, which also received SCTR support, the authors examined the expression of these genes in healthy pregnant women.

"Having observed the correlated expression of these genes in preeclampsia, we wanted to see the pattern of expression of these genes in normal pregnancy," said Lee. "We had a secondary goal of seeing whether vitamin D status affected the expression of these genes."

The sFLT1 protein interferes with the activity of vascular endothelial growth factor (VEGF), which is an important regulator of blood vessel development. This reduces vascular growth in the placenta. The amount of sFLT1 in the placenta is regulated in part by SAM68 and NKX2-5, also known as the tinman gene. This hypothesized NKX2-5/SAM68/sFLT1 gene "axis" may contribute to the development of preeclampsia.

"NKX2-5 might be controlling the regulation of sFLT1 and SAM68 in such a way that in preeclampsia, the expression levels of those genes go awry and tilt the vascular development in a direction that might trigger preeclampsia," said Lee.

Vitamin D affects many aspects of the mother's health during pregnancy. To investigate how the gene axis is affected by maternal vitamin D status, Lee's team studied placental samples from 43 pregnant women enrolled in a clinical trial at MUSC organized by their collaborator, MUSC Health neonatologist Carol L. Wagner, M.D., a professor in the Department of Pediatrics. Half of the women received a high dose of vitamin D3 (4,000 IU/day), and the other half received a placebo. The study group included African American, Hispanic American and Caucasian American women.

In contrast to their previous study, the team did not detect significant levels of NKX2-5 in placental tissue samples before a healthy delivery. This finding suggests that NKX2-5 expression is important in early at-risk pregnancies but not healthy pregnancies. However, the team did observe a strong positive correlation between SAM68 and sFLT1 in all study participants.

"The tight correlation between SAM68 and sFLT1 makes us think that there's a functional relationship between these genes," said Lee.

Interestingly, when assessed at the last visit before delivery, women who were vitamin D deficient (