**Deficiency of the hormone ELABELA causes pre-eclampsia in mice**

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Pre-eclampsia (PE) is the most common pregnancy-related disease. PE occurs during the third trimester and its symptoms comprise of high blood pressure (also referred to as hypertension) and high levels of protein excretion in urine (known as proteinuria). PE occurs in up to 8% of pregnancies and puts both the mother and child at serious risk for complications and sometimes death. A defective placenta is believed to be responsible for the disease as delivery of the baby and its placenta will resolve all symptoms. The exact origin of PE is not well understood, but it is accepted that in pre-eclamptic women, the fetus’ placenta is not fully functioning. In a healthy first trimester, placental cells, which are called trophoblasts, invade the maternal decidua that lines the uterus. By doing so, these specialized fetal cells remodel the maternal spiral arteries into vessels that can accommodate a large blood flow towards the developing fetus. In PE, the decidua is poorly invaded by trophoblasts and as a consequence spiral arteries remain narrow, leading to reduced levels of oxygen (known as hypoxia) and nutrients reaching the baby, which will lead to stunted growth.

ELABELA (ELA, www.elabela.com) is a very small secreted protein which was first discovered to control heart and vascular development (1). When injected in the bloodstream of adult rats, ELA was later found to have potent hypotensive and inotropic properties, meaning that it could readily lower blood pressure and increase heart contractility. This suggested that it could be protective against, and help recover from, heart failure (2,3). These functions appear to be mediated by one of ELA’s cell surface receptors known as the Apelin Receptor (APLNR). ELA possesses a second receptor which accounts for its activity in human embryonic stem cells and in ovarian cancer which both do not have APLNR (4, 5).

We sought to better understand the function of ELA during mammalian development. For this purpose we generated mutant mice in which ELA was no longer present. The embryos of these mice were smaller and displayed severe cardiovascular defects. In addition, their placentas were underdeveloped with significantly less blood vessels in the area where exchange of oxygen and nutrients takes place. This was very reminiscent of what is seen in women with PE.

Therefore, we examined whether ELA-deficient mice experienced gestational hypertension and proteinuria, the two landmark phenotypes of PE. Indeed, towards the end of pregnancy (in mice it only last 3 weeks), the blood pressure in ELA-deficient mice significantly rose along with proteinuria, both of which entirely resolved at parturition. In other words, pregnant mice lacking ELA represent a promising and novel model to study the development of PE.

Next, we checked whether it was possible to reverse the PE symptoms in these mice by giving them ELA as an injected drug. The daily administration of ELA was very efficient in alleviating the PE symptoms and increase the birth weight of the mouse pups born to these pregnant mice. This proof of concept indicates that ELA may become a viable therapeutic for treating PE.

To extend our findings to human, we next documented that ELA was indeed present in human placentas, and when added to cultured trophoblasts could instruct them to become more invasive. These are preliminary but encouraging results that ELA, or more precisely lack thereof, might lead to the development of PE in women.

Our paper provides a strong stepping stone towards the investigation of ELA as a hormone secreted by the placenta which is required for its proper development. It remains to be seen whether circulating levels of ELA in women’s blood could serve as a predictive biomarker, which is a significant unmet need for early diagnosis of women at risk of developing PE. Lastly, our work defines a possible therapeutic intervention window in which injection of the ELA hormone, like Insulin for diabetic patients, could serve to cure, or ameliorate the prognosis, of PE women and their developing babies.

**Original article:**

Ho L, van Dijk M, Chye STJ, Messerschmidt DM, Chng SC, Ong S, Yi LK, Boussata S, Goh GH, Afink GB, Lim CY, Dunn NR, Solter D, Knowles BB, Reversade B. ELABELA deficiency promotes preeclampsia and cardiovascular malformations in mice. Science. 2017 Aug 18;357(6352):707-713.

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