REPRODUCTIVE ENDOCRINOLOGY

ERR γ -PRE-ECLAMPSIA LINK STRENGTHENS

In a new study, Carole Mendelson and colleagues show that systolic blood pressure in pregnant mice is positively regulated by estrogen-related receptor γ (ERR γ), an orphan nuclear receptor highly expressed in the placenta. These findings might have implications in the management of pre-eclampsia, a hypertensive disorder of pregnancy characterized by placental dysfunction and associated with maternal and neonatal morbidity and mortality.

In their previous work, the team demonstrated that ERR γ functions as an O₂-sensitive transcription factor required for differentiation of placental trophoblasts—a key step in the physiological transformation of the spiral arteries in the initial phase of placentation. As placental hypoxia has a central role in the pathogenesis of pre-eclampsia, the researchers analysed the expression of ERR γ in term placentas from women with pre-eclampsia (with markedly elevated blood pressure) and gestation-matched normotensive women. ERR γ mRNA and protein levels were significantly upregulated in placentas from women with pre-eclampsia, compared with those from normotensive controls.

To further investigate the role of ERR γ during pregnancy, the researchers studied ERR γ -deficient mice. As ERR $\gamma^{-/-}$ mice die within the first 72 h of life, the team used ERR $\gamma^{+/-}$ pregnant mice that had been bred to genetically similar male mice. Maternal systolic blood pressure was significantly reduced in pregnant ERR $\gamma^{+/-}$ mice compared with wild-type pregnant mice; conversely, treatment of wild-type pregnant mice with an ERR γ agonist markedly increased systolic blood pressure. ERR γ haploinsufficiency was also associated with changes in the levels of proangiogenic and antiangiogenic factors and components of the renin–angiotensin–aldosterone system, which are factors known to be involved in the pathogenesis of pre-eclampsia.

“Collectively, these findings reveal a potential role of ERR γ in maternal blood pressure homeostasis during pregnancy and suggest that aberrant ERR γ expression may contribute to [the] pathogenesis of pre-eclampsia,” the researchers state in their report. As nuclear receptors are particularly amenable to small-molecule-based drug design, targeting ERR γ might be a promising approach to reduce hypertension in women with pre-eclampsia.

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