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RNA INTERFERENCE

Pre-empting preeclampsia

Preeclampsia is a hypertensive disorder of pregnancy that poses substantial risk to mothers and fetuses, and the only treatment option is early delivery of the fetus. Now, a study in *Nature Biotechnology* reports the development of small interfering RNA (siRNA) therapeutics that silence the placenta-derived mediators of preeclampsia and suppress clinical signs in a baboon model of the condition.

Preeclampsia arises owing to abnormally high serum levels of sFLT1 proteins — antiangiogenic factors secreted by the placenta that correspond to the soluble extracellular domain of vascular endothelial growth factor receptor 1 (VEGFR1). sFLT1 proteins scavenge circulating VEGF, which reduces VEGFR1 signalling and thereby causes maternal hypertension through various mechanisms.

Selective silencing of sFLT1 without affecting the full-length receptor is of crucial importance for therapeutic efficacy. Using transcriptional profiles of normal and preeclamptic placentas, the researchers had previously identified three major sFLT1 mRNA isoforms (sFLT1-i13 short, sFLT1-i13 long and sFLT1-e15a) that are upregulated in preeclamptic placentas and have unique 3′ ends.

In the current study, Turanov et al. designed a panel of 47 siRNAs that collectively targeted the three key sFLT1 mRNA isoforms. In vitro screening with luciferase-based reporters enabled the team to select the four most potent siRNA candidates.

To create siRNAs suitable for systemic delivery, compounds were fully chemically stabilized and conjugated to cholesterol. A Cy3 fluorescent dye was used for labelling.

Fluorescence microscopy revealed the siRNAs accumulated mainly in the liver, kidneys, spleen and placental labyrinth, consistent with the fenestrated architecture of these organs, and did not cross the placental barrier to the fetus. Intravenous or subcutaneous injection both resulted in approximately 7% accumulation of the siRNA dose in the placenta, which led to substantial silencing of target mRNAs.

Blood samples taken during the third trimester showed that sFLT1-targeted siRNA treatment substantially reduced circulating levels of sFLT1 compared with control pregnant mice. Importantly, treatment did not affect the survival or ability of pups to thrive.

Next, Turanov et al. turned to a baboon model of preeclampsia in which ligation of a single uterine artery cuts placental blood flow by ~30%, causing a surge in sFLT1 levels and maternal hypertension. Injection of the test siRNAs 1 h after arterial ligation caused a potent reduction in circulating sFLT1 compared with control animals, albeit with variable kinetics between treated animals. Approximately 2 weeks after injection, serum sFLT1 levels were reduced by more than 50% and remained at this level to the end of the protocol. Reduction in sFLT1 levels translated into normalization of blood pressure and proteinurea, which are key clinical manifestations of preeclampsia.

Overall, siRNA therapeutics could represent an easy to manufacture and cost-effective opportunity to selectively target sFLT1. The authors note that dosing will require careful titration as excessive blood pressure lowering could reduce uterine blood flow.

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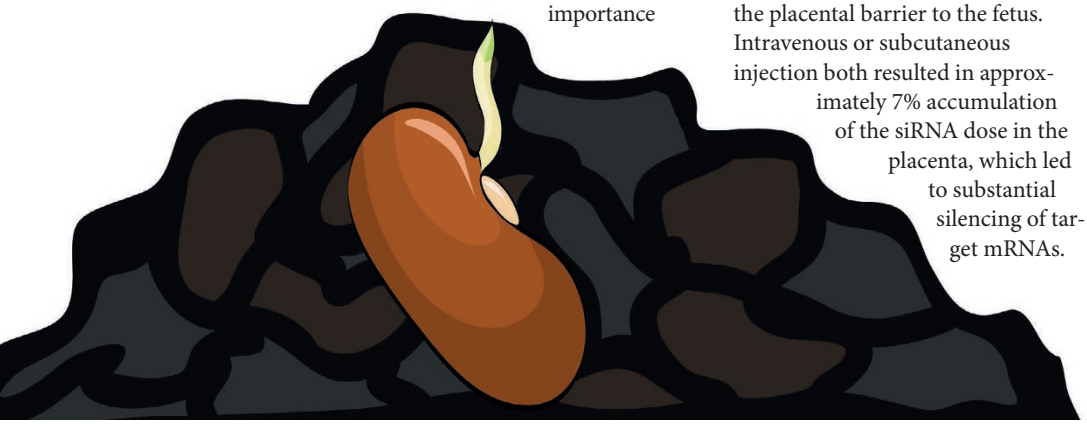

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