Exogenous microRNAs in maternal food pass through placenta, regulate fetal gene expression

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In a new study published in the *Protein & Cell*, Chen-Yu Zhang's group at Nanjing University reports that small non-coding RNAs in maternal food can transfer through placenta to regulate fetal gene expression.

MicroRNAs (miRNA) are a class of noncoding RNAs with lengths of approximately 22 nucleotides that bind to target messenger RNAs to inhibit protein translation. In previous studies, the same group has found that plant miRNAs can enter into the host blood and tissues via the route of food-intake. The food-derived exogenous miRNAs are absorbed, packaged into microvesical (MV) and then secreted into circulation by cells of animal GI tract. More importantly, once inside the host, the food-derived exogenous miRNAs can regulate host physiology by regulating host "target" genes in the cross-kingdom manner. In support of this new concept, they have also found a plant microRNA, MIR2911, which is enriched in honeysuckle, directly targets influenza A viruses (IAV) including H1N1, H5N1 and H7N9. Drinking of honeysuckle soup can prevent IAV infection and reduce H5N1-induced mice death.

Here, they report another surprising finding that exogenous plant miRNAs and artificial synthetic small influence RNAs (siRNAs) can transfer through the placenta and directly regulate fetus gene expression. Firstly, exogenous plant miRNAs was detected in human umbilical cord blood, amniotic fluid as well as animal foetuses with certain level. When pregnant mice were administrated honeysuckle soup (the exogenous

plant microRNAs are physiological concentration in food), the plant MIR2911 was detected in fetus liver with significant level. Finally, feeding pregnant mice with synthetic alpha-fetoprotein (AFP, only expressed in foetus liver) siRNA decreased significantly AFP mRNA and protein levels. They have further demonstrated that MV- driven small RNAs are able to pass through placenta.

This work is important for the following reasons:

1) This is the first time to demonstrate that small RNAs can pass through mammalian placenta and directly regulate foetus gene, consequently may also influence foetus development. It's well known that the placenta is a vital organ on which the survival and growth of the foetus are critically dependent. It forms the interface between the maternal and foetal environments, facilitating the exchange of gases, nutrients and waste products between the mother and baby, and also acts as a barrier against the maternal immune system. "The classical concept is that nucleic acid is not able to pass through the mammalian placenta, while we have also demonstrated that MV- driven small RNAs are able to pass through placenta", Zhang said. This discovery is obviously important to understand further the function of placenta and maternal and foetal environments.

2) Exogenous small RNAs in food not only affect pregnant female, but influence foetus development as well. The dietary patterns of the mother will influence the foetus or even determine the postnatal health status. Dietary bias or other unhealthy dietary habits would also affect the foetus health by disrupting the balance of transplacental miRNAs or even cause a foetus - origin adult disease.

3) This finding also reveals the possibility that maternal small-noncoding RNAs participate in fetal epigenetic regulation during pregnancy. Thus, the pathological status of the mother will result in an abnormal

endogenous miRNA profile per se, which will also influence foetal health.

"According to what I know, this is the first study to examine the transplacental transmission of small-noncoding RNAs." Professor Yali Hu said, who is an expert of department of Obstetrics and Gynecology, Nanjing Drum Tower Hospital. "This finding also proposes a brand new potential strategy to treat fetal diseases in utero. Given that artificial synthetic siRNAs can transfer through placenta, we can try to use gene therapy to treat fetal disease by maternal administration." Hu said.

More information: Li et al.: "Small non-coding RNAs transfer through mammalian placenta and directly regulate fetal gene expression" Publishing on *Protein & Cell*.

Provided by Nanjing University School of Life Sciences