miR-145 is associated with placental growth in mice
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Introduction

• Abnormal placental development and function can result in fetal growth restriction (FGR).
• FGR is associated with increased risk of infant morbidity and mortality and has life-long impacts on health.
• The insulin-like growth factor (IGF) axis is imperative for normal placental and hence fetal development.
• The actions of IGF1 and -II in regulating both human and murine placental growth and function are mediated by IGF1R (1, 2).
• Modulating expression of IGF1R in the placenta may improve placental growth and improve outcomes of pregnancies complicated by FGR.
• In the human placenta, microRNAs (miRs) regulate expression of components of the IGF axis (3, 4).
• One miR, miR-145, modulates human placental growth by targeting IGF1R (5), so it may be possible to utilise miR-145 based drugs to manipulate placental growth in humans.
• Prior to testing in humans, miR-based drugs would need to be tested in mice, however it is unclear whether miRs and specifically miR-145, influence placental and fetal growth in mice.

Hypotheses and Aims

Hypotheses:

• miR-145 is expressed in the mouse placenta
• miR-145 regulates murine placental and fetal growth by targeting IGF1R

Aims:

• To ascertain whether miR-145 is expressed in the mouse placenta and fetus
• To determine if miR-145 is associated with placental growth in mice by examining both placenta growth and miR-145 expression across gestation
• To determine the relationship between miR-145 expression and IGF1R in the mouse placenta and fetus

Methods

Pregnant C57BL/6J mice

QPCR confirms that miR-145 is expressed in the mouse placenta, and levels significantly increase (P<0.05) over gestation.

QPCR also demonstrated that IGF1R mRNA is expressed in the mouse fetus and this significantly decreases (P<0.005) over gestation.

However, QPCR confirms that IGF1R mRNA expression does not alter (P>0.05) in the mouse placenta over gestation.

IHC demonstrates that IGF1R is expressed throughout the placenta (decidua, junctional and labyrinth zones) in mice and protein expression appears to reduce with gestation.

• However, QPCR confirms that IGF1R mRNA expression does not alter (P>0.05) in the mouse placenta over gestation.

These results are consistent with results found in studies on the human placenta (1) and suggest that miR-145 may negatively regulate placental growth in mice.

1) miR-145 is expressed in murine placenta and inversely correlates with placental growth

miR-145 Expression - Fetus

miR-145 Expression - Placenta

Placental Proliferation (Ki67)

• QPCR demonstrated that miR-145 is expressed in the mouse fetus but does not alter with gestation.
• QPCR confirms that miR-145 is expressed in the mouse placenta, and levels significantly increase (P=0.05) over gestation.

• Analysis of cell proliferation (Ki67) reveals that proliferation significantly decreases (P<0.05) over gestation.

• These results are consistent with results found in studies on the human placenta (1) and suggest that miR-145 may negatively regulate placental growth in mice.

2) IGF1R is expressed in the fetus and placenta throughout gestation

• IHC demonstrates that IGF1R is expressed throughout the placenta (decidua, junctional and labyrinth zones) in mice and protein expression appears to reduce with gestation.

• However, QPCR confirms that IGF1R mRNA expression does not alter (P=0.05) in the mouse placenta over gestation.

These results are consistent with studies that have shown that miR-145 acts by reducing IGF1R protein and not mRNA expression (5).

• QPCR also demonstrated that IGF1R mRNA is expressed in the mouse fetus and this significantly decreases (P=0.005) over pregnancy.

Conclusions

• miR-145 is expressed in the mouse placenta and is significantly increased over gestation, similar to data observed in the human placenta (6).
• Proliferation significantly decreases over gestation in the mouse placenta, and inversely correlates with placental growth; this is also consistent with studies in the human placenta.
• There was no change in placental IGF1R mRNA throughout pregnancy, however IHC appears to demonstrate that IGF1R protein expression decreases towards term; this discrepancy between mRNA and protein expression is consistent with the known actions of miRs in the human placenta: data from this lab group suggests that miR-145 targets IGF1R protein degradation as opposed to repression of mRNA translation (4).
• These results combined suggests that miR-145 is likely to have similar actions in regulating placental growth in mice as it does in humans, however the role of miR-145 in regulating IGF1R expression in mice remains to be established.
• Ongoing work will examine the potential therapeutic role of miR-145 based drugs to improve placental and fetal growth using mouse models of FGR.

References