The role of NDRG1 in placental injury

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Fetal Growth Restriction
Pathophysiology of placental insufficiency

Placental Injury
Hypoxia

?

Fetal Growth Restriction
Hypoxic trophoblasts (in vitro)

IUGR placentas (in vivo)

Δ gene expression

Microarray

Δ gene expression

Microarray

NDRG1
N-myc Downstream Regulated Gene1

In vivo

In vitro

Does NDRG1 cause trophoblast dysfunction?

NDRG1 Silencing
- Differentiation $\downarrow$
- Cell Viability $\downarrow$
- Apoptosis $\uparrow$

NDRG1 Over-Expression
- Differentiation $\uparrow$

Ndurationg1-null mouse

- Neuropathic phenotype

Okuda, et al, 2004
Expression of *Ndrg1* in the mouse placenta

Kidney (WT)

Placenta (WT)

Placenta (KO)

NDRG1

Negative CTL
Breeding experiments

12% O₂
E12.5-18.5
E18.5 embryos and placentas

+/+
-/-
+/+
+/-
Embryo weights

Control

Hypoxia

Mean Embryo Weight (gm)

Male  Female

WT  Het  KO

Male  Female

WT  Het  KO

* *
Expected genotype distribution

+/-          +/-

+/-   +/-   -/-

+/-   +/-   -/-
Genotype distribution

Control

Hypoxia

WT  Het  KO

Male
Female

WT  Het  KO

Male
Female

Frequency

n: 25 68 30 32 63 35 37 84 35 44 87 16
Effect of *Ndrq1* deletion in hypoxic placentas

**Pathway Analysis**

- Lipid metabolism and transport
- Cholesterol metabolism
- LXR signaling
Liver X Receptor

- Nuclear receptor for oxysterols
  - Cholesterol accumulation
  - Oxidative stress
- Promotes cholesterol efflux and fatty acid synthesis
Effect of LXR ligands on human trophoblasts

Impaired differentiation

Cytotoxicity

Relative hCG secretion

Relative LDH in media

25OHC (μg/mL)

25OHC (μg/mL)
Lipid accumulation

CTL

T0901317

Lipid

Lipid + Nuclei
NDRG1 inhibits LXR-driven transcription in primary trophoblasts

Hypoxia

LXR Activation

NDRG1

CTL vector  NDRG1 vector
Fetal:Maternal Serum Cholesterol Ratio

Control

Hypoxia

Male
Female

Male
Female

WT
Het
KO

WT
Het
KO

Fetal/Maternal Serum Cholesterol Ratio

Male
Female

Male
Female

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Model of placental injury

Hypoxia

NDRG1

LXR Activation

Cytotoxicity
Impaired differentiation
Aberrant lipid metabolism

Placental Injury
Fetal Growth Restriction
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