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Does adaptation to high altitude affect hypoxia-dependent structural plasticity of the placenta?

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Does adaptation to high altitude affect hypoxia-dependent structural plasticity of the placenta?

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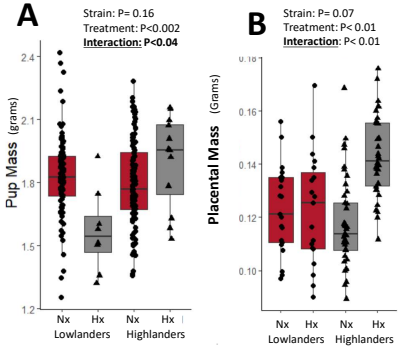
Introduction

- High altitude residence (>2500 m) causes fetal growth restriction (FGR) during pregnancy in lowland mammals.
- Highland-adapted humans and sheep do not experience this altitude-dependent FGR.
- The placenta is thought to be involved in protecting offspring from FGR.

Study System

- Deer mice (*Peromyscus maniculatus*) naturally occur across wide ranges of altitudes, and highland populations of deer mice have adaptations to adult physiology that improve survival and performance at altitude.
- As in humans, high altitude deer mice are protected from FGR during pregnancy **(Figure 1).**

Treatment Key: = Normoxia = Hypoxia



> Figure 1 Absence of hypoxia-dependent fetal growth restriction in highland deer mice is associated with larger placentas. **(A)** Whereas lowland deer mice experience growth restriction when gestated under chronic hypoxia (Hx), highland-adapted deer mice produce pups comparable in birth weight to those produced under normoxia (Nx). **(B)** Highland deer mice have larger placentas when gestated under hypoxia. Statistical analysis was performed using two-way ANOVAs in R version 4.0.3.

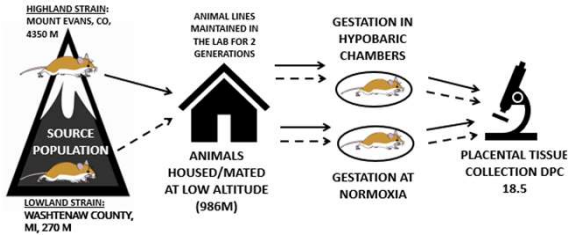
Hypothesis

- **Structural plasticity in the placenta in response to chronic hypoxia facilitates protection against FGR in highland-adapted deer mice.**

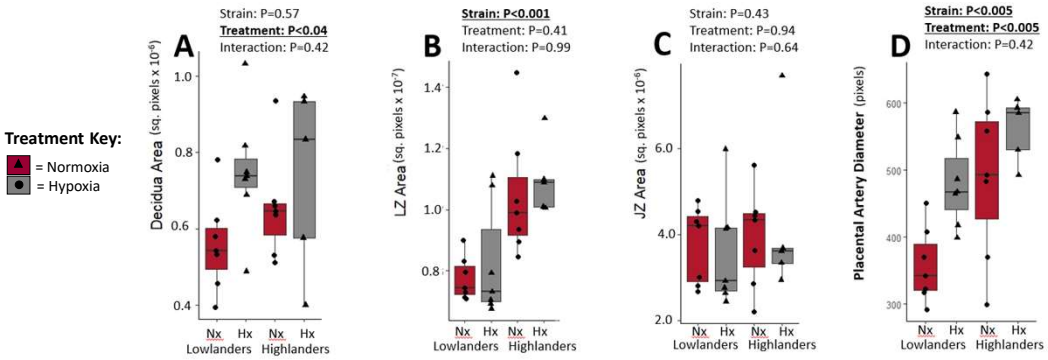
Methods

- We acclimated pregnant mice from lowland and highland populations to either normoxia or hypoxia from day 1 to day 18.5 of gestation **(Figure 2).**
- Placental tissue was collected from both strains on day 18.5 of gestation
- Immunohistochemistry (IHC) was used to label zones of the placenta so that we could quantify placental structures.

Figure 2



Results: Placenta structure is altered by chronic hypoxia and differs between strains



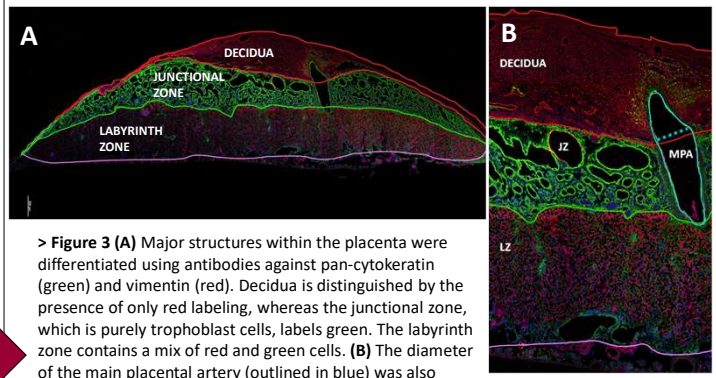
> Figure 4 Placental structure of *Peromyscus* varies with strain and treatment (hypoxia exposure during gestation). **[A]** Decidua area increases in response to hypoxia. **[B]** The LZ of highlanders is larger than that of lowlanders, regardless of treatment. **[C]** JZ area is not affected by stain or treatment. **[D]** Diameter of the main placental artery increased in response to hypoxia in both strains, however highlanders exhibited a larger main placental arteries compared with lowlanders in either treatment. Statistical analysis was performed using two-way ANOVAs in R version 4.0.3.

Immunohistochemistry

> Immunohistochemistry was used to label major structures within the rodent placenta

- **Main Placental Artery:** Brings maternal blood to placenta.
- **Decidua:** Maternal tissue, site of vascular remodeling.
- **Junctional Zone:** Contains invasive cell types that perform vascular remodeling, endocrine function.
- **Labyrinth Zone:** Contains highly branched villi, site of nutrient transfer between fetal and maternal systems.

> ImageJ software was used to quantify the area of junctional zone (JZ), labyrinth zone (LZ), and decidua of the placenta, and the diameter of the main placental artery (Fig 3).



> Figure 3 (A) Major structures within the placenta were differentiated using antibodies against pan-cytokeratin (green) and vimentin (red). Decidua is distinguished by the presence of only red labeling, whereas the junctional zone, which is purely trophoblast cells, labels green. The labyrinth zone contains a mix of red and green cells. **(B)** The diameter of the main placental artery (outlined in blue) was also measured at its widest point.

Conclusions and Future Directions

- **Main placental artery diameter shows plasticity in response to chronic hypoxia, whereas LZ size does not.**
  - A larger LZ in highlanders could contribute to improved fetal growth by increasing area across which nutrient and gas exchange can occur.
  - MPA diameter may contribute to improved blood flow in the placenta in both strains.
- **Lowlanders still experience FGR despite increasing main placenta artery diameter as a response to hypoxia.**
  - Increasing the MPA is not sufficient to protect against FGR.
- **Future Directions**
  - We will increase sample size to increase confidence in results.
  - Additional IHC analysis will be performed to quantify the area of the placenta allocated to gas and nutrient surfaces.

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