Placental Regional Variations in the Expression of VEGF, Its Receptors, and PLGF in Fetal Growth Restriction

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BACKGROUND

- Fetal growth restriction (FGR) is defined as growth at or below the 10th percentile.
- Maternal Causes of FGR include hypertension, diabetes, smoking, substance abuse, and malnutrition.
- FGR is associated with abnormal angiogenesis.
- The two main angiogenic factors are vascular endothelial growth factor (VEGF) and placental growth factor (PLGF).
- VEGF expression occurs early in placentation, which coincides with vasculogenesis and branching angiogenesis (1). Expression is stimulated by low pO_2 (2,3).
- PLGF expression occurs later and is associated with non-branching angiogenesis (4). Expression is stimulated by high pO_2 (2,3).
- There is an interrelationship between pO_2, VEGF and PLGF balance, and branching and non-branching angiogenesis (4).
- Previous studies conducted by this lab have demonstrated that expression of the two main angiogenic factors, VEGF and PLGF, exhibit higher expression in the periphery as compared to the central region of tissue from placentas of normal pregnancies.
- The goal of this study was to explore the differential expression of angiogenic factors and receptors in the center and periphery of fetal growth restricted placentas as compared to the results obtained from normal pregnancy placental samples.

References

1. Maulik D, et al. *Clinical Obstetric Gynecology.* 2006; 49:219-27.
2. Khaliq A, et al. *Lab Invest.* 1999; 79;151-70.
3. Tuder RM, et al. 1995; *J Clin Invest* 95: 1798–1807.
4. Regnault TRH, et al. *Physiology* 2003; 550:641-56.
5. 2. Kaufmann P, et al. *Placenta* 2004; 25:114-26.

RESULTS

- Immunoreactivity of VEGF was stronger in the center than in the periphery. The expressions of VEGFR1, VEGFR2, and PLGF were stronger in the periphery than in the center.

Figure 1. Immunoreactivity of VEGF was stronger in villi of the central region of the placenta.

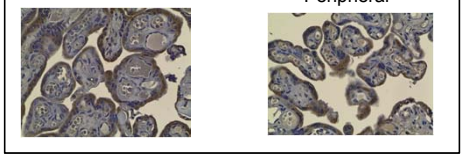


Figure 2. Immunoreactivity of VEGFR1 was stronger in villi of the peripheral region of the placenta.

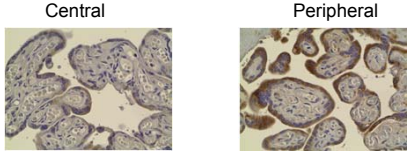


Figure 3. Immunoreactivity of VEGFR2 was stronger in villi of the peripheral region of the placenta.

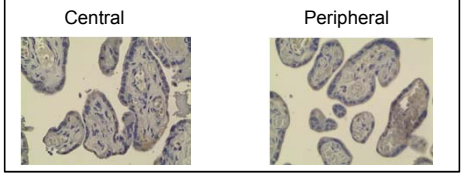
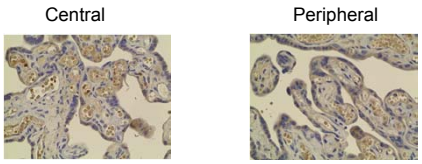


Figure 4. Immunoreactivity of PLGF was stronger in villi of the cetnral region of the placenta.



- Western blot results showed significantly higher expression of VEGF in the center than in the periphery. The expressions of VEGFR1, VEGFR2, and PLGF were higher in the periphery, though this finding was not significant for VEGFR2 (see table 1 below).

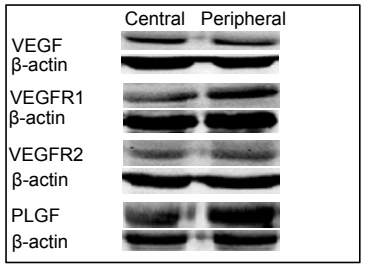


Table 1: Normalized Values for Western Blot Densiometric Data with β-Actin

Angiogenic Factors	Central	Peripheral	Significance
VEGF	0.237±0.018	0.188±0.019	0.001
VEGFR1	0.479±0.041	0.694±0.065	0.023
VEGFR2	0.226±0.049	0.262±0.061	0.080
PLGF	0.622±0.006	0.727±0.007	0.009

Normalization with β-actin corrects for loading error.
Normalized values of intensity are listed ± SEM.

METHODS

- A literature search was conducted using MEDLINE. The results were limited to articles and studies from 1995-present. Search terms included placenta, fetal growth retardation, vascular endothelial growth factor, vascular endothelial growth factor receptor, placental growth factor, and angiogenesis.
- Placental tissue was collected from the central and peripheral chorionic sites of FGR pregnancies (n=8, 34-40 weeks gestation). These samples were obtained at Truman Medical Center at Hospital Hill from pregnancies that met the criteria of FGR.
- The expression of VEGF, VEGF Receptor 1 (VEGFR1), VEGF Receptor 2 (VEGFR2), and PLGF were localized by immunohistochemistry and quantified by western blot.
- The significance of difference between the center and periphery of western blot was determined by student t-test with a p value <0.05 considered to be significant.

CONCLUSIONS

- The observed differential expression of VEGF, its receptors, and PLGF may provide an explanation for the molecular mechanism for abnormal angiogenesis in FGR placentas.
- We speculate that abnormal regional distribution of placental perfusion and the consequent differential oxygenation may be responsible for the observed anti- and pro-angiogenic gene expression.
- Unlike placental samples from normal pregnancies, the samples from the FGR placentas demonstrated greater staining of VEGF in the center as compared to the periphery.
- The results suggest that there is an increased angiogenic stimulus in the center of the placenta in FGR versus the periphery in normal pregnancies early in placentation.
- Placental sampling sites should be considered for placental angiogenic studies in the future as more exploration on the topic is warranted.