Regulators of Complement System Activation Increase with Placental Ischemia-induced Hypertension in Rat

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Abstract

Preeclampsia is characterized by new onset hypertension, resultant organ perfusion, and increased activation of complement, part of the innate immune system. In a model of placental ischemia-induced hypertension, we previously found that complement activation products C3a and C5a in hindlimb maternal hypertension. In this model, placental ischemia increases the expression of endogenous regulators that dampen complement activation. The current study evaluated complement activation in kidney and placenta comparing maternal hypertension in rats undergoing abdominal aortic constriction (AAC) with control rats. In this model, placental ischemia increases the expression of endogenous regulators that dampen complement activation. In placenta, complement regulators CDS5 and CDS9 have been shown to increase in placental ischemia in normal pregnancy, indicating upregulation to control excessive complement activation. In kidney, however, the expression of complement regulators has not been assessed. Thus, we hypothesized that increased complement activation following placental ischemia in rat leads to an increase in complement regulators in kidney and placenta.

Hypothesis

Increased complement activation following placental ischemia in rat leads to an increase in complement regulators in kidney and placenta.

Background & Rationale

Preeclampsia is a pregnancy specific condition characterized by:
- New onset hypertension and often proteinuria
- Abnormal placental development with reduced placental perfusion and ischemia

Complement System and Preeclampsia

- The complement system is part of the innate immune system
- Complement activation is greater in blood, placenta, and kidney in preeclamptic pregnancies compared to normal pregnancies (Buurma et al, 2012; Penning et al, 2015)
- In situ, our previous studies demonstrated that preventing complement activation attenuates placental ischemia-induced hypertension (Lügseg et al, 2013)

Complement System Regulators

- Complement regulators are endogenous membrane proteins that limit complement activation on "self"
- Preeclampsia, an increase in complement regulators in placenta has been shown in human pregnancy compared to normal pregnancy (Buurma et al, 2012)
- The net complement activation is determined by both the degree of activation of the pathway and the expression levels of endogenous regulators that dampen the activation

Model of Placental Ischemia

Placental ischemia decreased Crys and CDS9 message in placenta.

Experimental Design

Placental ischemia increased CDS5 and CDS9 message in kidney

Reduced uterine perfusion pressure (RUPP) model of placental ischemia-induced hypertension

On gestation day (GD) 14 (Sprague Dawley rat), maternal arterial clips were placed on the lower abdominal aorta and the ovarian artery to decrease blood flow to the placenta and increase maternal blood pressure on GD29.

Results

Net complement activation = Activation of pathway by stimulus - Dampering by endogenous regulators (Cry, CDS5, CDS9)

Complement Regulators shown in grey

References:


Conclusions

Placental ischemia-induced changes in complement regulators are dependent on the tissue type

Placenta

In preeclampsia, the data suggest that the decrease in endogenous regulators contribute to the decrease in complement activation as demonstrated by increased C3 deposition and circulating C3a.

Kidney

In kidney, the increase in complement regulators is sufficient to limit C3 deposition, suggesting that complement activation in kidney does not contribute to increased circulating C3a following placental ischemia.

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