Novel roles of histidine-rich glycoprotein in physiological placental development and in prevention of hypertensive disorders of pregnancy.

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Hypertensive disorders of pregnancy (HDP) is a pathological condition with hypertension and vascular endothelial cell dysfunction (inflammation) during the gestational period. Recently, it was reported that reduction level of plasma histidine-rich glycoprotein (HRG) in human pregnant patients was correlated with the HDP seriousness. HRG is an anti-inflammatory factor that controls the progression of systemic inflammatory pathology and mainly produced from liver. However, HRG functions in HDP pathology and perinatal physiology have been still unknown. In this study, we examined the involvement of plasma HRG on placental formation and hypertensive event during the gestational period using C57BL/6 mice and HRG gene-deficient (HRG KO) mice. Plasma HRG level was decreased during the gestational period in C57BL/6 mice. In addition, HRG reduction was restored at post-partum and did not depend on the HRG gene expression in liver. Hysterectomy to the gestational C57BL/6 mice also restored the plasma HRG level up to the normal level. When Human plasma-purified HRG was injected to C57BL/6 mice on nulliparity or gestation, biological half-time of the injected HRG was short in the gestational mice compared with the nulliparous mice. Moreover, HRG KO mice showed hypertension by the gestation, whereas rise in blood pressure did not observed in the gestational C57BL/6 mice. The gestational HRG KO mice had fetal growth disorder and placental hyperplasia. These results suggest that HRG may have a physiological function in the gestational period. Pregnant HRG KO mice may be a HDP-like pathological model that causes abnormalities in the placental formation mechanism controlled by HRG.