Original Article

DNA methylation of the glucocorticoid receptor gene promoter in the placenta is associated with blood pressure regulation in human pregnancy

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Background: Blood pressure (BP) regulation during pregnancy is influenced by hormones of placental origin. It was shown that the glucocorticoid system is altered in hypertensive pregnancy disorders such as preeclampsia. Epigenetic mechanism might influence the activity of genes involved in placental hormone/hormone receptor synthesis/action during pregnancy.

Method: In the current study, we analyzed the association of 5′-C-phosphate-G-3′ (CpG) site methylation of different glucocorticoid receptor gene (*NR3C1*) promoter regions with BP during pregnancy. The study was performed as a nested case-control study ($n = 80$) out of 1045 mother/child pairs from the Berlin Birth Cohort. Placental DNA was extracted and bisulfite converted. Nested PCR products from six *NR3C1* proximal promoter regions [glucocorticoid receptor gene promotor region B (GR-1B), C (GR-1C), D (GR-1D), E (GR-1E), F (GR-1F), and H (GR-1H)] were analyzed by next generation sequencing.

Results: NR3C1 promoter regions GR-1D and GR-1E had a much higher degree of DNA methylation as compared to GR-1B, GR-1F or GR-1H when analyzing the entire study population. Comparison of placental *NR3C1* CpG site methylation among hypotensive, normotensive and hypertensive mothers revealed several differently methylated CpG sites in the GR-1F promoter region only. Both hypertension and hypotension were associated with increased DNA methylation of GR-1F CpG sites. These associations were independent of confounding factors, such as family history of hypertension, smoking status before pregnancy and prepregnancy BMI. Assessment of placental glucocorticoid receptor expression by western blot showed that observed DNA methylation differences were not associated with altered levels of placental glucocorticoid receptor expression. However, correlation matrices of all *NR3C1* proximal promoter regions demonstrated different correlation patterns of intraregional and interregional DNA methylation in the three BP groups, putatively indicating altered transcriptional control of glucocorticoid receptor isoforms.

Conclusion: Our study provides evidence of an independent association between placental *NR3C1* proximal promoter methylation and maternal BP. Furthermore, we observed different patterns of *NR3C1* promoter methylation in normotensive, hypertensive and hypotensive pregnancy.

Keywords: DNA methylation, epigenetics, glucocorticoid receptor, hypertension, hypotension, *NR3C1* gene, placenta, pregnancy

Abbreviations: GR, glucocorticoid receptor; GR-1B, glucocorticoid receptor gene promotor region B; GR-1C, glucocorticoid receptor gene promotor region C; GR-1D, glucocorticoid receptor gene promotor region D; GR-1E, glucocorticoid receptor gene promotor region E; GR-1F, glucocorticoid receptor gene promotor region F; GR-1H, glucocorticoid receptor gene promotor region H; MAP, mean arterial blood pressure; *NR3C1*, glucocorticoid receptor gene

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) are a common pregnancy complication. HDP encompass several diseases, including chronic hypertension, gestational hypertension, preeclampsia and eclampsia [1]. According to the WHO, the prevalence of HDP is as high as 14% [2]. HDP is associated with adverse pregnancy outcomes for both, mother and fetus [3]. On the other hand, hypotension during pregnancy is also associated with impaired pregnancy outcomes [4].

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