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EPIGENETIC AND GENETIC ALTERATIONS OF THE PLACENTAL TUMOR-SUPPRESSOR GENE RARRES1 DURING HUMAN PLACENTOGENESIS

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Objectives: Human placental development is a suitable model for tumorigenesis, due to the invasive potential of fetal trophoblasts. Tumor-suppressor genes play important regulatory roles in both processes. Promoter hypermethylation and loss of the tumor-suppressor Rarres1 was shown to contribute to cancer progression due to increased invasiveness of tumor cells. Dysregulation of placental invasiveness is of etiopathological relevance for the development of intra-uterine growth restriction (IUGR). Our study investigated the epigenetic regulation of Rarres1 at different stages of gestation in healthy and IUGR placentas.

Methods: We determined the placental Rarres1 localisation using immunohistochemistry. Rarres1 expression was analysed by sqRT-PCR in placental samples and choriocarcinoma cell-lines. Rarres1 promoter methylation pattern analysis and SNP genotyping was performed by pyrosequencing of DNA from 125 placental tissues and 4 trophoblast-like cell-lines.
Result: Rarres1 expression was localised to the syncytiotrophoblast, extravillous and villous trophoblasts. The Rarres1 promoter was differentially methylated in an ATG-proximal (10%) and -distant region (80%) and showed an overall hypermethylation pattern in choriocarcinoma cell lines (50-95%). DNA of first trimester placental tissues was hypomethylated within both analyzed promoter regions. We detected the SNP rs6441224 in the Rarres1 promoter and determined a significant correlation of the genotype with the percentage of methylation of two proximate CpGs. This methylation was significantly reduced in IUGR placentas along with a significant increase of the T/T genotype by 20%.
Conclusion: Our study is the first to characterise Rarres1 in functional placental compartments. We revealed a region-specific, as well as gestational age-specific promoter methylation pattern. The loss of heterozygosity and the decrease of methylation in IUGR placentas might point to a dysregulation of Rarres1 during gestation in these patients. Our study underscores the importance of tumor-suppressor genes for placental development and might help to further understand the pathogenesis of IUGR and other placental diseases like preeclampsia.