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ABSTRACTS BOOK

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HYPOTHYROIDISM PRODUCES CHANGES IN THE UTERINE VASCULATURE DURING THE IMPLANTATION PROCESS

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Hypothyroidism is one of the most common endocrine abnormalities implicated in the recurrent loss of pregnancy. Our laboratory, have shown that hypothyroidism in the rat is associated with a lower number of pups per litter due to a lower number of implantation sites and a decrease in the proliferation of the endothelial and decidual cells during the process of implantation of the embryo. On the other hand, is known that angiogenesis is a critical process in the uterine endometrium for embryo implantation, maintenance of early pregnancy, and development of the placenta. During this period, steroid hormones (E2 and P4) stimulate the synthesis of vascular endothelial growth factor (VEGF-A), the main modulator of angiogenesis during peri-implantation period. Therefore we hypothesize that hypothyroidism affects the normal vascularization of endometrium during implantation. The aim of this work was to study the effect of hypothyroidism on the degree of vascularization of the uterine decidua during the implantation process. Hypothyroidism was induced in female Wistar rats by daily administration of 6-propyl-2-thiouracil (PTU) 0,1 g/L in drinking water. In addition, hormone replacement therapy with T3 was administered simultaneously to the treatment with PTU (PTU+T3), in daily physiological doses of 0.6ug/100g. Both groups were compared to rats that only drink tap water (Control),on day five (G5) and seven (G7) of gestation. Uterine vascularization was evaluated by immunofluorescence. Besides,mRNA expression of PECAM (Platelet endothelial cell adhesion molecule, an indicator of the presence of endothelial cells) and VEGF-A were evaluated during the same peri-implantation periods (G5 y G7)by RTqPCR. Our results demonstrate that hypothyroidism decreases vascularization density of the uterine tissue during the process of implantation of the embryo ($p<0.05$). On the other hand, our results demonstrated a significant increase of expression of VEGF mRNA when hypothyroid rats were treated with T3 before implantation, in comparison to the control group and hypothyroid group ($p< 0.05$). However, no changes were found in the levels of PECAM expression among the different groups. In conclusion, the failure of implantation due to hypothyroidism may be directly linked to expression of VEGF-A, and consequently to vascularization of the endometrium before implantation in early gestation. Although are necessary further studies that corroborate the exact mechanism, our results identify molecular targets regulated by thyroid hormones that may link hypothyroidism to implantation failure and recurrent miscarriage.

GENERAL, CELLULAR AND MOLECULAR BIOLOGY

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LONG-TERM HIPOTHYROIDISM PRODUCES MAMMARY GENETIC AND EPIGENETIC CHANGES

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The mammary tissue is one of the few ones whose terminal differentiation is completed in adult life through lactation. In this process, the mammary genome is subject to epigenetic modifications that result in the selective expression of differentiation-associated genes and the establishment of the mammary transcriptome. After weaning, massive involution occurs and the tissue returns to a pregestation-like stage. This proliferation, differentiation and apoptosis cycle is regulated by lactogenic, ovarian and thyroid hormones. Thyroid pathologies such as hypothyroidism (hypoT) have an impact on the lactoma (lactation transcriptome), impairing the mammary epithelial cell ability to express differentiation genes. Despite this, the long-term impact of hipoT on mammary gland, and if hypoT alters the mammary epithelial cell epigenome are both unknown. To determine the long-term hypoT impact on mammary transcriptome, we used female virgin Sprague Dawley rats of 55 and 130 days old without treatment, female 130 day old rats that underwent a cycle of pregnancy, lactation and involution without treatment and a PTU treated 130 day old female rats that underwent a cycle of pregnancy, lactation and involution. Using real-time PCR, we evaluated the mRNA expression levels of differentiation-associated genes, such as GATA-3, PINC, NCOA-1, NCOA-2, and STAT6; and by methyl-specific PCR (MSPCR) we analyzed the methylation of two promoter regions of STAT6 gene. The analysis of gene expression showed that the long-term hypoT altered the mammary transcriptome differentially and that it had a special impact on NCOA-2, a gene associated with histones modification. Also, hypoT changed the mRNA expression of two mammary epithelial differentiation-associated genes, STAT6 and GATA3, both related to alveolar development. In addition, the methylation analysis