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Aberrant Acetylation/Methylation of Homeobox (HOX) Family Genes in Cumulus Cells of Infertile Women with Polycystic Ovary Syndrome (PCOS)

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Abstract : Introduction: Polycystic Ovary Syndrome is a common gynecologic disorder. Many factors including environment, metabolism, hormones and genetics are involved in etiopathogenesis of PCOS. Of genes that have altered expression in human reproductive system disorders are HOX family genes which act as transcription factors in regulation of cell proliferation, differentiation, adhesion and migration. Since recent evidences consider epigenetic factors as causative mechanisms of PCOS, evaluation of association between known epigenetic marks of acetylation/methylation of histone 3 (H3K9ac/me) with regulatory regions of these genes can represent better insight about PCOS. In the current study, cumulus cells (CCs) which have critical roles during folliculogenesis, oocyte maturation, ovulation and fertilization were aimed to monitor epigenetic alterations of HOX genes. Material and methods: CCs were collected from 20 PCOS patients and 20 fertile women (18-36 year) with male infertility problems referred to the Royan Institute to have ICSI under GnRH antagonist protocol. Informed consents were obtained from the participants. Thirty six hours after hCG injection, ovaries were punctured and cumulus oocyte complexes were dissected. Soluble chromatin were extracted from CCs and Chromatin Immune precipitation (ChIP) coupled with Real Time PCR was performed to quantify the epigenetic marks of histone H3K9 acetylation/methylation (H3K9ac/me) on regulatory regions of 15 members of HOX genes from A-D subfamily. Results: Obtained data showed significant increase of H3K9ac epigenetic mark on regulatory regions of HOXA1, HOXB2, HOXC4, HOXD1, HOXD3 and HOXD4 ($P < 0.01$) and HOXC5 ($P < 0.05$) and also significant decrease of H3K9ac into regulatory regions of HOXA2, HOXA4, HOXA5, HOXB1 and HOXB5 ($P < 0.01$) and HOXB3 ($P<0.05$) in PCOS patients vs. control group. On the other side, there was a significant decrease in incorporation of H3K9me level on regulatory region of HOXA2, HOXA3, HOXA4, HOXA5, HOXB3 and HOXC4 ($P\leq0.01$) and HOXB5 ($P < 0.05$) in PCOS patients vs. control group. This epigenetic mark (H3K9me2) has significant increase on regulatory region of HOXB1, HOXB2, HOXC5, HOXD1, HOXD3 and HOXD4 ($P \leq 0.01$) and HOXB4 ($P < 0.05$) in patients vs. control group. There were no significant changes in acetylation/methylation levels of H3K9 on regulatory regions of the other studied genes. Conclusion: Current study suggests that epigenetic alterations of HOX genes can be correlated with PCOS and consequently female infertility. This finding might offer additional definitions of PCOS, and eventually provides insight for novel treatments with epidrugs for this disease.

Keywords : epigenetic, HOX genes, PCOS, female infertility
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