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Involvement of estrogen in testicular functions through epigenetic mechanisms

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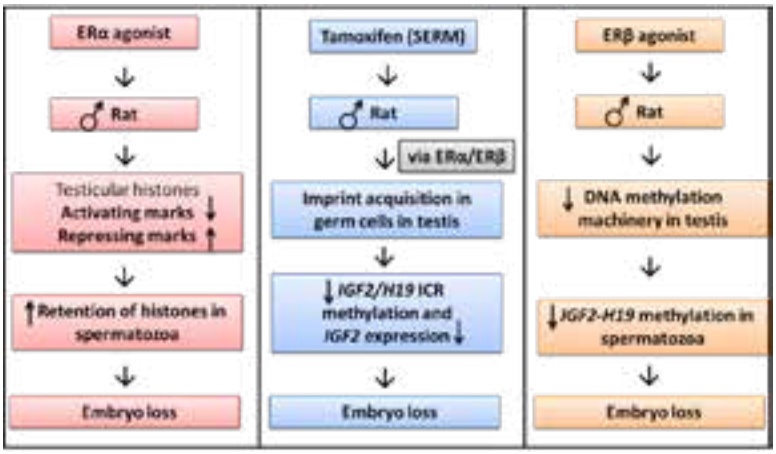
Statement of the Problem: Estrogen, the traditional female hormones, is involved in male fertility. Presence of the two estrogen receptors (α and β) in testicular cells and sterility due to their absence, points to a role of estrogen in spermatogenesis. However, the mechanism of action of the two estrogen receptors (ERs) is not yet clear. Recent studies have demonstrated that estrogen can affect epigenetic mechanisms. Studies were done in our laboratory reported, decrease in male fertility in rats due to increase in embryo loss, upon paternal tamoxifen, a selective ER modulator (SERM) treatment. A significant decrease in methylation level of the paternally imprinted Igf2-H19 DMR was observed, which correlated with the extent of post-implantation embryo loss. Hence, estrogen signaling could be involved in imprint acquisition in the male germ cells. Tamoxifen can act through both the ERs, hence the reduction in fertility observed after these treatments would be the cumulative effects brought about by both the receptors. There is little information on the individual roles of the two ERs in spermatogenesis through epigenetic mechanism and their contribution towards the maintenance of fertility. The present study was undertaken to understand the epigenetic mechanisms affected through the two ERs in spermatogenesis and correlate it to fertility.

Methodology: Using ER-subtype specific agonist treatment model in adult male rats, epigenetic changes, i.e. DNA methylation and histone modification and retention in the testicular cells and spermatozoa was done.

Findings: Both the ER agonist increased embryo loss, however through different epigenetic mechanism. ERα agonist affected histone modification in testicular cells and increased retained histones in spermatozoa, ERβ agonist affected DNA methylation transferases in the testis and decreased methylation at Igf2-H19 DMR in spermatozoa.

Conclusion & Significance: The two ERs affect different epigenetic mechanisms in the testis, thereby affecting the sperm epigenome leading to embryo loss. The study highlights mechanism/s through which xenoestrogens could affect male fertility



Recent Publications

1. Dumasia K, Kumar A, Deshpande S and Balasinor N H (2017) Estrogen signaling, through estrogen receptor β, regulates DNA methylation and its machinery in male germ line in adult rats. Epigenetics 12(6):476-483
2. Dumasia K, Kumar A, Deshpande S, Sonawane S and Balasinor N H (2016) Differential roles of estrogen receptors, ESR1 and ESR2, in adult rat spermatogenesis. Molecular and Cellular Endocrinology 428: 89-100.
3. Neelam Kedia, Leena Kadam, Kushaan Dumasia and Balasinor N H (2016) Possible Role of Paternal Aberrant

Imprinting in Placental Development: A Study in Tamoxifen Treatment Rat Model. Journal of Clinical Epigenetics 2:1

4. Kumar A, Dumasia K, Deshpande S and Balasinor N H Direct regulation of genes involved in sperm release by estrogen and androgen through their receptors and coregulators. J Steroid Biochem Mol Biol. 171:66–74
5. Kumar A, Dumasia K, Deshpande S, Gaonkar R and Balasinor N H (2016) Actin related protein complex subunit 1b controls sperm release, barrier integrity and cell division during adult rat spermatogenesis. Biochimica et Biophysica Acta 1863:1996–2005.

Biography

Nafisa Huseni Balasinor has made significant contribution in the field of hormonal regulation of male fertility. Using tamoxifen treated rat models, they have demonstrated the role of estrogen in acquisition and maintenance of genomic imprint marks during spermatogenesis. Her group has shown the importance of paternal aberrant imprinting in causing post implantation embryo loss in rats and humans and affecting placentation in rat model. These studies have immense significance in understanding paternal involvement of paternal in early embryo growth and placentation. In addition, they are studying the role of estrogen in the process of sperm release from testis in adult rats. Understanding the molecular mechanism sperm release may help in identifying novel targets for male fertility regulation. These studies also elucidate the mechanism through which endocrine disruptors like xenoestrogens may affect male germ line and cause compromised male fertility.

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