

# BÖLÜM 5

## Erkek Fertilitesinin Düzenlenmesinde Leydig ve Sertoli Hücre Fonksiyonlarının Regülasyonu

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### LEYDİĞ HÜCRELERİ

Spermatogenez ve spermiyogenez basamaklarının gerçekleştiği testis iki anatomik bölgeden oluşur. Bu bölgeler seminifer tübüller ve interstisyel alan denen kompartmanlardan meydana gelir. Seminifer tübüller içinde farklı aşamalarda germ hücreleri yer alır. Ayrıca destek hücreleri olan sertoli hücreleri de bu bölgede yerleşir. Seminifer tübüller arasındaki vaskülarize alan ise interstisyel bölgeyi oluşturur (1). İnterstisyel bölge içinde, androjen salgı yapan Leydig hücreleri bulunmaktadır ve bu hücreler, hipotalamik-hipofiz eksenini tarafından hormonal düzenleme altındadır. Adını 1850 yılında alman anatomist zoolog Franz von Leydig'den alan Leydig hücreleri; seminifer tübüllerin etrafındaki interstisyel dokuda (kan ve lenf damarları etrafında) düzensiz hücre kümeleri şeklinde yerleşmişlerdir. (2).

### *Leydig Hücre Kökeni ve Histolojisi*

Testiküler hacmin yaklaşık üçte biri interstisyel alandan oluşur. Bu alan leydig hücreleri, kan damarları, sinir ağı, lenfatikler, bağ doku ve makrofajlara ev sahipliği yapar. Yetişkin bir insan testisinde yaklaşık 700 milyon Leydig hücresi bulunup, bu sayı interstisyel dokunun yaklaşık %10-20'sini oluşturur. Poligonal

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TDF bölgesi varsa embriyo erkek, aksi halde dişi yönünde gelişme gösterecektir. Sekizinci haftadan itibaren testiste Leydig hücreleri testosteron ve insülin benzeri faktör 3 salgılanmaya başlarken sertoli hücreleride AMH üretmeye başlar ve böylece bu hormonun yardımıyla, çift cinsiyetlilik gibi durumlar engellenmiş olur.

## KAYNAKLAR

1. Haolin C, Yiyan W, Renshan G, Barry RZ Leydig cell stem cells: Identification, proliferation and differentiation *Mol Cell Endocrinol* 2017; 445:65-73.
2. Massimo DF, Susanna D From testis to teratomas: a brief history of male germ cells in mammals. *Int J Dev Biol.* 2013; 57:115-21.
3. Seguchi H , Hadziselimovic F Electron microscopic investigation on the postnatal development of human Leydig cells. *Acta Anat (Basel)* 1982;112 (3):254-63.
4. Paniagua R, Nistal M, J. Sáez F, Fraile B Ultrastructure of the aging human testis. *Journal of Electron Microscopy* 1991; 19 (2): 241-260.
5. Holm M, Rajpert-De Meyts E, Andersson AM, Skakkebaek NE. Leydig cell micronodules are a common finding in testicular biopsies from men with impaired spermatogenesis and are associated with decreased testosterone/LH ratio. *JPathol* 2003;199 (3): 378-386.
6. Ivell R, Wade JD, Anand-Ivell R INSL3 as a Biomarker of Leydig Cell Functionality. *Biology of Reproduction* 2013; 88 (6): 147, 1-8.
7. Choi Y, Lee EG, Lee G, Jeong MG, Kim HK Amodiaquine promotes testosterone production and de novo synthesis of cholesterol and triglycerides in Leydig cells. *J. Lipid Res.* 2021; 62: 100152.
8. King Steven, Stocco DM Steroidogenic acute regulatory protein expression in the central nervous system *Frontiers in Endocrinology* 2011; 2 (72):1-4.
9. A.Lefèvre E, Rogier C, Astraudo C, Duquenne C. Finaz Regulation by retinoids of luteinizing hormone/chorionic gonadotropin receptor, cholesterol side-chain cleavage cytochrome P-450, 3 $\beta$ -hydroxysteroid dehydrogenase/ $\Delta^{5-4}$ -isomerase and 17 $\alpha$ -hydroxylase/C<sub>17-20</sub> lyase cytochrome P-450 messenger ribonucleic acid levels in the K9 mouse Leydig cell line. *Molecular and Cellular Endocrinology* 1994;106 (1-2), 31-39.
10. Moore A, Chen CL, Davis JR, Morris ID. Insulin-like growth factor-I mRNA expression in the interstitial cells of the rat testis. *J Mol Endocrinol* 1993;11:319-324.
11. Bornstein SR, Rutkowski H, Vrezas I Cytokines and steroidogenesis. *Molecular and Cellular Endocrinology* 2004; 215 (1-2), 135-141.
12. Li L , Wang Y, Li X, Liu S , Wang G , Lin H , Zhu Q, Guo J, Chen H , Ge HS, Ge RS. Regulation of development of rat stem and progenitor Leydig cells by activin. *Andrology* 2017; 5 (1), 125-132.
13. P. Hardy M, Haolin C, Ge RS, R. Zirkin B Leydig cells: From stem cells to aging. *Molecular and Cellular Endocrinology* 2009; 306 (1-2), 9-16.
14. Min C, Xiaona W, Yanbo W, Lianjun Z, Binyang X, Limin L, Xiuhong C, Wei L, Fei G *Wt<sub>1</sub>* Is Involved in Leydig Cell Steroid Hormone Biosynthesis by Regulating Paracrine Factor Expression in Mice. *Biology of Reproduction* 2014; 90 (71), 1-9.
15. Whitehouse AJO, Zulqarnain Gilani S, Shafait F, Mian A, Weiting Tan D, Maybery MT et al. Prenatal testosterone exposure is related to sexually dimorphic facial morphology in adulthood. *Proc Biol Sci.* 2015; 282 (1816): 1-9.

16. Lui WY, Mruk D, Lee WM, Cheng CY Sertoli Cell Tight Junction Dynamics: Their Regulation During Spermatogenesis. *Biology of Reproduction* 2003; 68 (4),1087–1097.
17. Yang Y, Han C GDNF stimulates the proliferation of cultured mouse immature Sertoli cells via its receptor subunit NCAM and ERK1/2 signaling pathway. *BMC Cell Biology* 2010; 11 (78),1-10.
18. Wong WJ, Khan YS Histology, Sertoli Cell. StatPearls [Internet] StatPearls Publishing; Treasure Island (FL): Aug 19, 2020.
19. Hai Y, Hou J, Liu Y, Liu Y, Yang H, Li Z, He Z The roles and regulation of Sertoli cells in fate determinations of spermatogonial stem cells and spermatogenesis. *Seminars in Cell & Developmental Biology* 2014; (29), 66-75.
20. Xu HY, Zhang HX, Xiao Z, Qiao Jie , Li Rong Regulation of anti-Müllerian hormone (AMH) in males and the associations of serum AMH with the disorders of male fertility. *Asian J Androl.* 2019; 21 (2): 109–114.
21. Anna C. Erickson, John R. Couchman Still More Complexity in Mammalian Basement Membranes. *The Journal of Histochemistry & Cytochemistry* 2000 ;48 (10): 1291–1306.
22. Piprek RP, Kolasa M, Podkowa D, KlocJacek M, Kubiak Z et al. Cell adhesion molecules expression pattern indicates that somatic cells arbitrate gonadal sex of differentiating bipotential fetal mouse gonad. *Mechanisms of Development* 2017; (147), 17-27.
23. Johnson Larry, Thompson DL, Varner DD Role of Sertoli cell number and function on regulation of spermatogenesis *Animal Reproduction Science Volume* 2008 105 (1–2):23-51.
24. Nistal M , Paniagua R, González-Peramato P Perspectives in Pediatric Pathology, Chapter 4. Pubertal and Adult Testis 2015,18 ( 3):187-202.
25. Arenas IM, Lobo V.T Maria, Enrique Caso, Lidia Huerta, Paniagua Ricardo, Marti n-Hidalgo MA Normal and pathological human testes express hormone-sensitive lipase and the lipid receptors CLA-1/SR-BI and CD36. *Human Pathology* 2004; 35 (1), 34-42.
26. Cheng CY, Mruk DD Cell Junction Dynamics in the Testis: Sertoli-Germ Cell Interactions and Male Contraceptive Development. *fizyol Rev* 2002; 82: 825-874.
27. Nakanishi Y, Shiratsuchi A Phagocytic Removal of Apoptotic Spermatogenic Cells by Sertoli Cells: Mechanisms and Consequences *Biol. Pharm. Bull.* 2004 ; 27 (1), 13-16.
28. Marifke J, Sandlow J. Anatomy and Physiology of Androgen Regulation in Men. *Clinical Urologic Endocrinology* 2012;1–9.
29. Liang J, Li H, Mei J, Cao Z, Tang Y Sertoli cell-derived exosome-mediated transfer of miR-145-5p inhibits Leydig cell steroidogenesis by targeting steroidogenic factor 1. *The FASEB Journal.* 2021;35: 1-12.
30. Nascimento AR, TaliariPimenta M, Lucas TFG, Catarina CR, Porto S et al. Intracellular signaling pathways involved in the relaxin-induced proliferation of rat Sertoli cells *European Journal of Pharmacology* 2012; 69 (11–3): 283-291.
31. Samy ET, Li JC, Grima J, Lee WM, Silvestrini B, Cheng CY. Sertoli cell prostaglandin D2 synthetase is a multifunctional molecule: its expression and regulation. *Endocrinology.* 2000;141:710-21.
32. Carreau S. Paracrine control of human Leydig cell and Sertoli cell functions. *Folia Histochem Cytobiol.* 1996;34:111-9.
33. Cyr DG. Connexins and pannexins: Coordinating cellular communication in the testis and epididymis. *Spermatogenesis.* 2011;1:325-38.
34. Brehm R, Zeiler M, Rüttinger C, Herde K, Kibschull M, et al. sertoli cell-specific knockout of connexin43 prevents initiation of spermatogenesis. *Am J Pathol.* 2007;171:19-31.

35. Fumel B, Guerquin MJ, Livera G, Staub C, Magistrini M et al. Thyroid Hormone Limits Postnatal Sertoli Cell Proliferation In Vivo by Activation of Its Alpha1 Isoform Receptor (TRAlp-ha1) Present in These Cells and by Regulation of Cdk4/JunD/cmyc mRNA Levels in Mice. *Biol Reprod.* 2012;87:16.
36. Boyer A, Yeh JR, Zhang X, Paquet M, Gaudin A, et al. CTNNB1 signaling in sertoli cells downregulates spermatogonial stem cell activity via WNT4. *PLoS One.* 2012;7:29764.
37. Zhang J, Wong CH, Xia W, Mruk DD, Lee NPY et al. Regulation of Sertoli-Germ Cell Adherens Junction Dynamics via Changes in Protein-Protein Interactions of the N-Cadherin- $\beta$ -Catenin Protein Complex which Are Possibly Mediated by c-Src and Myotubularin-Related Protein 2: An *in Vivo* Study Using an Androgen Suppression Model *Endocrinology.* 2005; (146), 3 (1):1268–1284.
38. Blasco V, Pinto FM, González-Ravina C, Santamaría-López E, Luz Candenas et al. Tachykinins and Kisspeptins in the Regulation of Human Male Fertility. *J. Clin. Med.* 2020; 9: 113.
39. Gualtieri AE, Mazzone GL, Rey RA, Schteingart HF. FSH and bFGF stimulate the production of glutathione in cultured rat Sertoli cells. *Int J Androl.* 2009;32 (3):218-25.
40. Riera MF, Meroni SB, Schteingart HF, Pellizzari EH, Cigorraga SB Regulation of lactate production and glucose transport as well as of glucose transporter 1 and lactate dehydrogenase A mRNA levels by basic fibroblast growth factor in rat Sertoli cells *J Endocrinol.* 2002;173 (2):335-43.
41. Cayli S, Ocakli S, Erdemir F, Tas U, Aslan H, Yener T, Karaca Z. Developmental expression of p97/VCP (Valosin-containing protein) and Jab1/CSN5 in the rat testis and epididymis. *Reprod Biol Endocrinol.* 2011;19 (9):117.
42. Rebourcet D, O’Shaughnessy PJ, Smith LB. The expanded roles of Sertoli cells: lessons from Sertoli cell ablation models *Current Opinion in Endocrine and Metabolic Research* 2019; 6: 42-48.
43. Zhou M, He HJ, Tanaka O, Sekiguchi M, Kawahara K, Abe H. Different localization of ATP sensitive K<sup>+</sup> channel subunits in rat testis. *Anat Rec Hoboken.* 2011;294:729-37.
44. Rato L, Socorro S, Cavaco JE, Oliveira PF. Tubular fluid secretion in the seminiferous epithelium: ion transporters and aquaporins in Sertoli cells. *J Membr Biol.* 2010;236:215- 24.
45. Gonçalves R, Zamoner A, Zanatta L, Zanatta AP, Pertile Remor A et al. 1,25 (OH)<sub>2</sub> vitamin D<sub>3</sub> signalling on immature rat Sertoli cells: gamma-glutamyl transpeptidase and glucose metabolism. *Journal of Cell Communication and Signaling* 2017; 11: 233–243.
46. Auharek SA, Avelar GF, Lara NL, Sharpe RM, França LR. Sertoli cell numbers and spermatogenic efficiency are increased in inducible nitric oxide synthase mutant mice. *Int J Androl.* 2011;34:621-9.
47. Wu H, Wang H, Xiong W, Chen S, Tang H, Han D. Expression patterns and functions of toll-like receptors in mouse sertoli cells. *Endocrinology.* 2008;149:4402-12.
48. Rato Luís, Alves MG, Socorro S, Duarte AI et al. Metabolic regulation is important for spermatogenesis. *Nature Reviews Urology* 2012;9:330–338.
49. Bergadá I, Milani C, Bedecarrás P, et al. Time course of the serum gonadotropin surge, inhibitors, and anti-Müllerian hormone in normal newborn males during the first month of life. *The Journal of Clinical Endocrinology & Metabolism.* 2006;91 (10):4092-4098.
50. Hiort O, Holterhus PM The molecular basis of male sexual differentiation. *European Journal of Endocrinology* 2000; 142:101–110.