

Bölüm 10

ENDOMETRİOZİS PATOGENEZİNDE GÜNCEL KONSEPTLER

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Bu bölümde endometriozis oluşumunda ileri sürülen yeni hipotezlerin ayrıntılı anlatımına yer verilmiştir. Endometriotik odak gerçekten steroid sentez edebilen bir yapı mıdır ve gerçekten aromataz enzim aktivitesine sahip midir? Bu bölüm aracılığı ile NF-kB yolları ve demirin etyolojide suçlanmasına neden olan mekanizmaların öğrenilmesi, dioxin, konjenital uterin anomalilerde ileri sürülen hipotezlerin yetersizliği, heterolog ve homolog modeller, müllerianozis ve aberan peritoneal çevre gibi birçok konudaki bilgilerimizi güncellemize ve bilimsel çalışmalarımıza yön vermemize olanak sağlayacaktır. **Editorial**

Giriş

- Teoriler (Sampson, Çöломik metaplazi, Lenföjen /Hematojen yayılım)
- Kök hücre teorisi
- Mülleriiosis (Müllerianozis)
- Neden Sampson teorisi olamaz?
- Genetik/OXEGENE
- Dioksinin rolü
- Ötopik endometriyumun farkları
- Ötopik ve ektopik endometriyumda mikromRNA'nın değişken ekspresyonu
- Endometriozisli kadınların ötopik endometriyumundaki farklı proteom profili
- Anormal uterin kontraksiyon
- TNF bağımlı apoptoz indükleyici ligand (TRAIL) aktivitesi

- Aberan peritoneal çevre
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- Th2 hücreler
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- Mast hücre aracılı mekanizmalar
- Adiponektin
- Endometriozis ve NF-kB yolağı
- Makrofajlarda NF-kB, demir ve oksidatif stres
- NF-kB inhibitörleri ve endometriozis
- Hormonal faktörler ve Steroidogenezis
- Siklooksijenaz 2 (COX-2)
- Aromataz knockout yapılırsa odaklar ne olur?
- Demir ve Endometriozis
- Toll Like Receptor (TLR), Fibronektin, Okside LDL
- Endometriozis kök hücre orjinli olabilir mi?
- Endometriozis etyopatogenezi araştırmalarında hangi hayvan modelini kullanalım?
- Mürin modelleri, Homolog modeller, Heterolog modeller
- Ektopik endometrial odaklarda progesteron rezistansını gösteren bir homolog fare modeli
- RU-486 ve GnRH α kullanımı

Giriş

Endometriozisin patofizyolojisi ve etiyolojisi tam olarak açıklanamamıştır. Sampson'a göre retrograd menstrüel akım ile peritonea taşınan endometrial debrisler burada implante olarak lezyonları meydana getirmektedir. Sampson'un teorisi olan geri ka-

Kaynaklar

1. Brosens I. Endometriosis rediscovered? *Hum Reprod.* 2004 Jul;19(7):1679-80
2. Nap AW, Groothuis PG, Demir AY, Evers JL, Dunselman GA. Pathogenesis of endometriosis. *Best Pract Res Clin Obstet Gynaecol.* 2004 Apr;18(2):233-44. Review.
3. Nisolle M, Donnez J. Peritoneal endometriosis, ovarian endometriosis, and adenomyotic nodules of the rectovaginal septum are three different entities. *Fertil Steril.* 1997 Oct;68(4):585-96. Review.
4. Sampson JA. Metastatic or Embolic Endometriosis, due to the Menstrual Dissemination of Endometrial Tissue into the Venous Circulation. *Am J Pathol.* 1927 Mar;3(2):93-110.43
5. Sasson IE, Taylor HS. Stem cells and the pathogenesis of endometriosis. *Ann N Y Acad Sci.* 2008 Apr;1127:106-15.
6. Benagiano G, Brosens I. History of adenomyosis. *Best Pract Res Clin Obstet Gynaecol.* 2006 Aug;20(4):449-63.
7. Knapp VJ. How old is endometriosis? Late 17th- and 18th-century European descriptions of the disease. *Fertil Steril.* 1999 Jul;72(1):10-4.
8. Batt RE, Smith RA. Embryologic theory of histogenesis of endometriosis in peritoneal pockets. *Obstet Gynecol Clin North Am.* 1989 Mar;16(1):15-28.
9. Batt RE, Smith RA, Buck Louis GM, Martin DC, Chapron C, Koninckx PR, Yeh J. Müllerianosis. *Histol Histopathol.* 2007 Oct;22(10):1161-6. Review.
10. Redwine DB. Mülleriosis instead of endometriosis. *Am J Obstet Gynecol.* 1987;156(3):761.
11. Signorile PG, Baldi F, Bussani R, D'Armiento M, De Falco M, Baldi A. Ectopic endometrium in human fetuses is a common event and sustains the theory of müllerianosis in the pathogenesis of endometriosis, a disease that predisposes to cancer. *J Exp Clin Cancer Res.* 2009 Apr 9;28:49.
12. Lauchlan SC. The secondary müllerian system revisited. *Int J Gynecol Pathol.* 1994 Jan;13(1):73-9.
13. Bulun SE. Endometriosis. *N Engl J Med.* 2009 Jan 15;360(3):268-79.
14. Batt RE, Mitwally MF. Endometriosis from thelarche to midteens: pathogenesis and prognosis, prevention and pedagogy. *J Pediatr Adolesc Gynecol.* 2003 Dec;16(6):337-47. Review.
15. Redwine DB. Was Sampson wrong? *Fertil Steril.* 2002 Oct;78(4):686-93. Review.
16. Redwine DB. Does a "peritoneal circulation" really exist? *Gynecol Obstet Invest.* 2003;55(2):63-7.
17. Díez García R, Prieto Díez M, Aguilar Tremoya F. Neonatal ovarian endometriosis. Its conservative treatment. *An Esp Pediatr.* 1996 Apr;44(4):397-8
18. Ebert AD, Fuhr N, David M, Schnepffel L, Papadopoulos T. Histological confirmation of endometriosis in a 9-year-old girl suffering from unexplained cyclic pelvic pain since her eighth year of life. *Gynecol Obstet Invest.* 2009;67(3):158-61.
19. Marsh EE, Laufer MR. Endometriosis in premenarcheal girls who do not have an associated obstructive anomaly. *Fertil Steril.* 2005 Mar;83(3):758-60.
20. Balci O, Karatayli R, Capar M. An incidental coexistence of Mayer-Rokitansky-Kuster-Hauser syndrome with pelvic ectopic kidney and perirenal endometrioma. *Saudi Med J.* 2008 Sep;29(9):1340-1.
21. Enatsu A, Harada T, Yoshida S, Iwabe T, Terakawa N. Adenomyosis in a patient with the Rokitansky-Kuster-Hauser syndrome. *Fertil Steril.* 2000 Apr;73(4):862-3.
22. Yan CM¹, Mok KM. Uterine fibroids and adenomyosis in a woman with Rokitansky-Kuster-Hauser syndrome. *J Obstet Gynaecol.* 2002 Sep;22(5):561-2.
23. Parkar RB, Kamau WJ. Images in endoscopy. Laparoscopic excision of bilateral functioning noncommunicating and rudimentary uterine horns in a patient with Mayer-Rokitansky-Küster-Hauser syndrome and pelvic endometriosis. *J Minim Invasive Gynecol.* 2009 Sep-Oct;16(5):522-4.
24. D'Hooghe TM. Invisible microscopic endometriosis: how wrong is the sampson hypothesis of retrograde menstruation to explain the pathogenesis of endometriosis? *Gynecol Obstet Invest.* 2003;55(2):61-2.
25. Bukulmez O, Hardy DB, Carr BR, Word RA, Mendelson CR. Inflammatory status influences aromatase and steroid receptor expression in endometriosis. *Endocrinology.* 2008 Mar;149(3):1190-204
26. Sebastian S, Bulun SE. A Highly Complex Organization of the Human CYP19 (Aromatase) Gene Revealed by the Human Genome Project. *The Journal of Clinical Endocrinology & Metabolism*, 2006; 86: 4600-4602.
27. Velasco I, Ación P, Campos A, Ación MI, Ruiz-Maciá E. Interleukin-6 and other soluble factors in peritoneal fluid and endometriomas and their relation to pain and aromatase expression. *J Reprod Immunol.* 2010 Mar;84(2):199-205
28. Beinke S, Ley SC. Functions of NF-kappaB1 and NF-kappaB2 in immune cell biology. *Biochem J.* 2004; 382 (Pt 2): 393-409. Review.
29. Chen LF, Greene WC. Shaping the nuclear action of NF-kappaB. *Nat Rev Mol Cell Biol.* 2004; 5: 392-401. Review.
30. Pahl HL. Activators and target genes of Rel/NF kappaB transcription factors. *Oncogene.* 1999; 18:6853-66. Review.
31. Karin M, Yamamoto Y, Wang QM. The IKK NF-kB system: a treasure trove for drug development. *Nat Rev Drug Discov* 2004; 3:17-26.

32. Hoffmann A, Baltimore D. Circuitry of nuclear factor kB signaling. *Immunol Rev* 2006; 210:171–86.
33. P. Viatour, M.P. Merville, V. Bours and A. Chariot: Phosphorylation of NF-kappa B and I-kappa B proteins: implications in cancer and inflammation. *Trends Biochem Sci* 30, 43-52 (2005)
34. J.C. Lousse, S. Defrère, R. González Ramos, A. Van Langendonck, S. Colette and J. Donnez: Involvement of iron, nuclear factor-kappa B (NF-kappa B) and prostaglandins in the pathogenesis of peritoneal endometriosis-associated inflammation: a review. *J Endometr* 1, 19-29 (2009)
35. Barrier BF, Kendall BS, Ryan CE, Sharpe-Timms KL. HLA-G is expressed by the glandular epithelium of peritoneal endometriosis but not in eutopic endometrium. *Hum Reprod*. 2006;21:864–869.
36. Simpson JL, Bischoff F. Heritability and candidate genes for endometriosis. *Reprod Biomed Online*. 2003 Sep;7(2):162-9. Review.
37. Kennedy S. Is there a genetic basis to endometriosis? *Semin Reprod Endocrinol*. 1997; 15(3): 309-18.
38. Simpson JL, Elias S, Malinak LR, Buttram VC Jr. Heritable aspects of endometriosis. I. Genetic studies. *Am J Obstet Gynecol*. 1980 Jun 1; 137(3): 327-31.
39. Rier SE, Turner WE, Martin DC, Morris R, Lucier GW, Clark GC. Serum levels of TCDD and dioxin-like chemicals in Rhesus monkeys chronically exposed to dioxin: correlation of increased serum PCB levels with endometriosis. *Toxicol Sci*. 2001 Jan;59(1):147-59.
40. Aisen P, Leibman A, and Zweier J. Stoichiometric and site characteristics of the binding of iron to human transferrin. *J Biol Chem* 1978; 253: 1930–1937.
41. Grossmann JG, Neu M, Evans RW, Lindley PF, Appel H, and Hasnain SS. Metal-induced conformational changes in transferrins. *J Mol Biol* 1993; 229: 585–590.
42. Grossmann JG, Neu M, Pantos E, Schwab FJ, Evans RW, Townes-Andrews E, Lindley PF, Appel H, Thies WG, and Hasnain SS. X-ray solution scattering reveals conformational changes upon iron uptake in lactoferrin, serum and ovo-transferrins. *J Mol Biol* 1992; 225: 811–819.
43. Collawn JF, Stangel M, Kuhn LA, Esekogwu V, Jing SQ, Trowbridge IS, and Tainer JA. Transferrin receptor internalization sequence YXRF implicates a tight turn as the structural recognition motif for endocytosis. *Cell* 1990; 63: 1061–1072.
44. Ward RJ, Wilmet S, Legssyer R, Crichton RR. The influence of iron homeostasis on macrophage function. *Biochem Soc Trans*. 2002;30:762-5.
45. MacKenzie EL, Iwasaki K, Tsuji Y. Intracellular iron transport and storage: from molecular mechanisms to health implications. *Antioxid Redox Signal*. 2008;10(6):997-1030. Review.
46. Beaumont C, Delaby C. Recycling iron in normal and pathological states. *Semin Hematol* 2009; 46: 328–338.
47. Nemeth E, Ganz T. Regulation of iron metabolism by hepcidin. *Annu Rev Nutr* 2006; 26: 323–342.
48. Donovan A, Lima CA, Pinkus JL, Pinkus GS, Zon LI, Robine S, Andrews NC. The iron exporter ferroportin/Slc40a1 is essential for iron homeostasis. *Cell Metab* 2005; 1: 191–200.
49. Soe-Lin S, Apte SS, Andriopoulos B Jr, Andrews MC, Schranzhofer M, Kahawita T, Garcia-Santos D, Ponka P. Nramp1 promotes efficient macrophage recycling of iron following erythrophagocytosis in vivo. *Proc Natl Acad Sci USA* 2009; 106: 5960–5965.
50. Golan A, Winston RM and Dargenio R (1984). Experimental endometriosis: a microsurgical animal model in rats. *Isr J Med Sci* 20,1094–1096.
51. Greenberg LH and Slayden OD (2004). Human endometriotic xenografts in immunodeficient RAG-2/gamma(c)KO mice. *Am J Obstet Gynecol* 190,1788–1795; discussion 1795–1796.
52. Grow DR, Williams RF, Hsiu JG and Hodgen GD (1996). Antiprogesterin and/or gonadotropin-releasing hormone agonist for endometriosis treatment and bone maintenance: a 1-year primate study. *J Clin Endocrinol Metab* 81,1933–1939.
53. Grummer R, Schwarzer F, Bainsczyk K, Hess-Stump H, Regidor PA, Schindler AE and Winterhager E (2001). Peritoneal endometriosis: validation of an in vivo model. *Hum Reprod* 16,1736–1743.
54. Taylor HS, Arici A, Olive D, Igarashi P. HOXA10 is expressed in response to sex steroids at the time of implantation in the human endometrium. *J Clin Invest* 1998; 101:1379–1384.
55. Taylor HS, Igarashi P, Olive DL, Arici A. Sex steroids mediate HOXA11 expression in the human perimplantation endometrium. *J Clin Endocrinol Metab* 1999; 84:1129–1135.
56. Satokata I, Benson G, Maas R. Sexually dimorphic sterility phenotypes in Hoxa10-deficient mice. *Nature* 1995; 374:460–463.
57. Benson GV, Lim H, Paria BC, Satokata I, Dey SK, Maas RL. Mechanisms of reduced fertility in Hoxa-10 mutant mice: uterine homeosis and loss of maternal Hoxa-10 expression. *Development* 1996; 122:2687–2696.
58. Hsieh-Li HM, Witte DP, Weinstein M, Branford W, Li H, Small K, et al. Hoxa 11 structure, extensive antisense transcription, and function in male and female fertility. *Development* 1995; 121:1373–1385.
59. González-Ramos R, et al, Involvement of the nuclear factor-kB pathway in the pathogenesis of endometriosis. *Fertil Steril* 2010;94:1985–94.
60. Cynthia X. Ma et al. Human Aromatase: Gene Resequencing and Functional Genomics (*Cancer Res* 2005; 65(23): 11071-82)
61. Kajihara H et al. New insights into the pathophysiology of endometriosis: from chronic inflammation to danger signal. *Gynecological Endocrinology*, 2010; Early Online, 1–7

62. Khan KN et al. Immunopathogenesis of pelvic endometriosis: role of hepatocyte growth factor, macrophages and ovarian steroids. *Am J Reprod Immunol.* 2008 Nov;60(5):383-404.
63. Hirata J, Kikuchi Y, Imaizumi E et al. Endometriotic tissues produce immunosuppressive factors. *Gynecologic and Obstetric Investigation* 1994; 37: 43–47.
64. Hirata T, Osuga Y, Yoshino O, Hirota Y, Harada M, Takemura Y, Morimoto C, Koga K, Yano T, Tsutsumi O et al. (2005). Development of an experimental model of endometriosis using mice that ubiquitously express green fluorescent protein. *Hum Reprod* 20,2092–2096.
65. Lousse JC et al. Iron storage is significantly increased in peritoneal macrophages of endometriosis patients and correlates with iron overload in peritoneal fluid. *Fertil Steril.* 2009 May;91(5):1668-75.
66. Velasco I et al. Interleukin-6 and other soluble factors in peritoneal fluid and endometriomas and their relation to pain and aromatase expression. *J Reprod Immunol.* 2010 Mar;84(2):199-205.
67. Bukulmez O, Hardy DB, Carr BR, Word RA, Mendelson CR. Inflammatory status influences aromatase and steroid receptor expression in endometriosis. *Endocrinology.* 2008 Mar;149(3):1190-204.
68. Fang Z, Yang S, Gurates B, Tamura M, Simpson E, Evans D, Bulun SE. Genetic or enzymatic disruption of aromatase inhibits the growth of ectopic uterine tissue. *J Clin Endocrinol Metab.* 2002 Jul;87(7):3460-6.
69. Hoffmann A, Natoli G, Ghosh G. Transcriptional regulation via the NF-kappaB signaling module. *Oncogene.* 2006 Oct 30;25(51):6706-16. Review.
70. Humar M et al. Barbiturates directly inhibit the calmodulin/calceineurin complex: a novel mechanism of inhibition of nuclear factor of activated T cells. *Mol Pharmacol.* 2004 Feb;65(2):350-61.
71. Luo JL, Maeda S, Hsu LC, Yagita H, Karin M. Inhibition of NF-kappaB in cancer cells converts inflammation-induced tumor growth mediated by TNFalpha to TRAIL-mediated tumor regression. *Cancer Cell.* 2004 Sep;6(3):297-305.
72. Beinke S, Ley SC. Functions of NF-kappaB1 and NF-kappaB2 in immune cell biology. *Biochem J.* 2004 Sep 1;382(Pt 2):393-409. Review.
73. Jono H et al. NF-kappaB is essential for induction of CYLD, the negative regulator of NF-kappaB: evidence for a novel inducible autoregulatory feedback pathway. *J Biol Chem.* 2004 Aug 27;279(35):36171-4.
74. Celik O et al. Surgical removal of endometrioma decreases the NF-kB1 (p50/105) and NF-kB p65 (Rel A) expression in the ectopic endometrium during the implantation window. *Reprod Sci.* 2013 Jul;20(7):762-70.
75. González-Ramos R, Defrère S, Devoto L. Nuclear factor-kappaB: a main regulator of inflammation and cell survival in endometriosis pathophysiology. *Fertil Steril.* 2012;98:520-8.
76. Viatour P, Merville MP, Bours V, Chariot A. Phosphorylation of NF-kappaB and IkappaB proteins: implications in cancer and inflammation. *Trends Biochem Sci.* 2005 Jan;30(1):43-52. Review.
77. Signorile PG et al. Ectopic endometrium in human fetuses is a common event and sustains the theory of müllerianosis in the pathogenesis of endometriosis, a disease that predisposes to cancer. *J Exp Clin Cancer Res.* 2009 Apr 9;28:49.
78. Signorile PG, Campioni M, Vincenzi B, D'Avino A, Baldi A. Rectovaginal septum endometriosis: an immunohistochemical analysis of 62 cases. *In Vivo.* 2009;23(3):459-64.
79. Lauchlan SC. The secondary müllerian system revisited. *Int J Gynecol Pathol.* 1994 Jan;13(1):73-9. Review.
80. Bulun SE, et al. Steroidogenic factor-1 and endometriosis. *Mol Cell Endocrinol.* 2009 Mar5;300(1-2):104-8.
81. Bulun SE. Endometriosis. *N Engl J Med.* 2009 Jan 15;360(3):268-79. Review.
82. D'Hooghe TM. Immunomodulators and aromatase inhibitors: are they the next generation of treatment for endometriosis? *Curr Opin Obstet Gynecol.* 2003;15(3):243-9. Review.
83. Parkar RB, Kamau WJ. Images in endoscopy. Laparoscopic excision of bilateral functioning noncommunicating and rudimentary uterine horns in a patient with Mayer-Rokitansky-Küster-Hauser syndrome and pelvic endometriosis. *J Minim Invasive Gynecol.* 2009 Sep-Oct;16(5):522-4.
84. Batt RE, Mitwally MF. Endometriosis from the larvae to midteens: pathogenesis and prognosis, prevention and pedagogy. *J Pediatr Adolesc Gynecol.* 2003 Dec;16(6):337-47. Review.
85. Díez García R, Prieto Díez M, Aguilar Tremoya F. [Neonatal ovarian endometriosis. Its conservative treatment]. *An Esp Pediatr.* 1996;44(4):397-8. Review.
86. Marsh EE, Laufer MR. Endometriosis in premenarcheal girls who do not have an associated obstructive anomaly. *Fertil Steril.* 2005;83(3):758-60.
87. Balci O, Karatayli R, Capar M. An incidental coexistence of Mayer-Rokitansky-Kuster-Hauser syndrome with pelvic ectopic kidney and perirenal endometrioma. *Saudi Med J.* 2008;29(9):1340-1.
88. Enatsu A, Harada T, Yoshida S, Iwabe T, Terakawa N. Adenomyosis in a patient with the Rokitansky-Kuster-Hauser syndrome. *Fertil Steril.* 2000 Apr;73(4):862-3.
89. Yan CM, Mok KM. Uterine fibroids and adenomyosis in a woman with Rokitansky-Kuster-Hauser syndrome. *J Obstet Gynaecol.* 2002;22(5):561-2.