

Bölüm 9

ENDOMETRİOZİS UPDATE

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ÜNİTE 2

Bilinmeyenlerle dolu endometriozis puzzle'ının çözümüne, yapacakları bilimsel çalışmalar ile katkıda bulunmak isteyen genç akademisyenlerin bilgilerini güncellemeleri ve yeni çalışma dizaynlarına yardımcı olması için okunması tavsiye edilen bir bölümdür. **Editorial**

Giriş

Endometriozis veya endometrioma hastası olan kadınların endometriyumları (ötopik endometrium) sağlıklı olanların endometriyumlarından (normal endometrium) farklıdır. Bu sebeple, endometriyumun fonksiyonel özelliklerinin endometriozis'e bağlı infertilitenin etyopatogenezinde önemli bir role sahip olduğu, gittikçe daha fazla kabul gören bir gerçektir. Peritoneal veya ovarian yerleşimli olmasına rağmen bu hastalığın primer etki alanlarından birisi beklide en önemlisi endometriumdur. Ötopik endometriyumda meydana gelen sekonder değişikliklerin klinik önemi ise yapılan son çalışmalara kadar bilinmemekteydi. Önceki çalışmalar daha çok hayvansal modellerde yapılmış ve saptanan ötopik endometrial değişiklikler insanlara uyarlanmaya çalışılmıştı.

Maymun veya rodentlerde yapılan endometriyozun modellerinde, ötopik endometriyumda invazyon, anjiyogenez, metilasyon, hücre büyümesi, immünomodülasyon ve steroid hormon yapımında görev alan çeşitli proteinlerin ekspresyonunun bozulduğu saptanmıştır. Bu veriler gösteriyor ki,

endometriotik odaklar ya da endometriomalar yerleşim alanlarından bağımsız olarak, ötopik endometriyumda çeşitli gen ekspresyonlarını değiştiren sinyal iletim yollarını aktive edebilme yeteneğindedirler. Bunu progesteron aracılıklı bir inflamatuvar yanıt oluşturarak veya hedef endometriyal hücrelerin epigenetik yapısını farklı metilasyon basamaklarında değiştirerek başarıyor olabilirler. Bizim çalışmamızda endometriomalı hastaların ötopik endometriyumlarında inflamasyonun major modülatörü olan NF-kB'nin ekspresyonundaki değişiklik klinik olarak insanlarda ilk defa saptanmış ve endometriozis cerrahisinin sadece odakları veya overdeki kistleri yok etmekle kalmayıp ötopik endometriyum da olumlu yönde düzelttiği saptanmıştır (Celik O, Reproductive Science, 2012). Yine ekibimiz tarafından yapılan diğer bir çalışmada ötopik endometriumlarda normal endometriumlara göre implantasyon genlerinde belirgin değişiklik saptanmış ve endometrioma cerrahisinin bu gen değişimlerini olumlu yönde değiştirdiği saptanmıştır (Celik O, unpublished data). Konuyla ilgili gen haritalarının bir kısmı ilk defa bu bölüm içerisinde bilgilerinize sunulacaktır.

Endometriyumun Histopatolojik Analizi

1990'da Fedele ışık ve elektron mikroskopunu kullanarak endometriozisi olan infertil kadınlarda endometriyumda yapısal değişiklikler olduğunu

Kaynaklar

1. Celik O, Celik E, Turkcuoglu I, Yilmaz E, Ulas M, Simsek Y, Karaer A, Celik N, Aydin NE, Ozerol I, Unlu C. Surgical removal of endometrioma decreases the NF-kB1(p50/105) and NF-kB p65 (Rel A) expression in the eutopic endometrium during the implantation window. *Reprod Sci.* 2013 Jul;20(7):762-70.
2. Bromer, J.G., Aldad, T.S., Taylor, H.S., 2009. Defining the proliferative phase defect. *Fertil. Steril.* 91, 698–704.
3. Jones, C.J., Inuwa, I.M., Nardo, L.G., Litta, P., Fazleabas, A.T., 2009. Eutopic endometrium from women with endometriosis shows altered ultrastructure and glycosylation compared to that from healthy controls—a pilot observational study. *Reprod. Sci.* 16, 559–572.
4. Brosens, I et al. The eutopic endometrium in endometriosis: are the changes of clinical significance? *Reproductive BioMedicine Online* (2012), doi:10.1016/j.rbmo.2012.01.022.
5. Fedele L, Marchini M, Bianchi S, Dorta M, Arcaini L, Fontana PE. Structural and ultrastructural defects in preovulatory endometrium of normo-ovulating infertile women with minimal or mild endometriosis. *Fertil Steril* 1990;53:989–993.
6. Hascalik S, Celik O, Kekilli E, Elter K, Karakas HM, Aydin NE. Novel noninvasive detection method for endometriosis: research and development of scintigraphic survey on endometrial implants in rats. *Fertil Steril.* 2008 Jul;90(1):209-13. Epub 2007 Jul 26.
7. Sarac K, Celik O, Hascalik S, Alkan A, Mizrak B. In vivo proton magnetic resonance spectroscopy in the evaluation of the endometrium. *Acta Obstet Gynecol Scand.* 2004 Aug;83(8):751-7.
8. Celik O, Hascalik S, Sarac K, Meydanli MM, Alkan A, Mizrak B. Magnetic resonance spectroscopy of premalignant and malignant endometrial disorders: a feasibility of in vivo study. *Eur J Obstet Gynecol Reprod Biol.* 2005 Feb 1;118(2):241-5.
9. Cunha-Filho JS, Gross JL, Lemos NA, Brandelli A, Castillos M, Passos EP. Hyperprolactinemia and luteal insufficiency in infertile patients with mild and minimal endometriosis. *Horm Metab Res* 2001;33:216–220.
10. Moeloek FA, Moegny E. Endometriosis and luteal phase defect. *Asia Oceania J Obstet Gynaecol* 1993;19:171–176.
11. Ordi J, Creus M, Casamitjana R, Cardesa A, Vanrell JA, Balasch J. Endometrial pinopode and alpha v beta 3 integrin expression is not impaired in infertile patients with endometriosis. *J Assist Reprod Gene* 2003;20:465–473.
12. Bourlev, V., Volkov, N., Pavlovitch, S., Lets, N., Larsson, A., Olovsson, M., 2006. The relationship between microvessel density, proliferative activity and expression of vascular endothelial growth factor-A and its receptors in eutopic endometrium and endometriotic lesions. *Reproduction* 132, 501–509.
13. Hey-Cunningham, A.J., Ng, F.W., Busard, M.P.H., Berbic, M., Manconi, F., Young, L., Zevallos, H.B.-V., Fraser, I.S., 2010. Uterine lymphatic and blood microvessels in women with endometriosis through the menstrual cycle. *J. Endometriosis* 2, 197–204.
14. Taylor, H.S., Bagot, C., Kardana, A., Olive, D., Arici, A., 1999. HOX gene expression is altered in the endometrium of women with endometriosis. *Hum. Reprod.* 14, 1328–1331.
15. Taylor, R.N., Yu, J., Torres, P.B., Schickedanz, A.C., Park, J.K., Mueller, M.D., Sidell, N., 2009. Mechanistic and therapeutic implications of angiogenesis in endometriosis. *Reprod. Sci.* 16, 140–146.
16. Rogers, P.A., Donoghue, J.F., Walter, L.M., Girling, J.E., 2009. Endometrial angiogenesis, vascular maturation, and lymphangiogenesis. *Reprod. Sci.* 16, 147–151.
17. Rogers, P.A.W., Abberton, K.M., 2003. Endometrial arteriogenesis: vascular smooth muscle cell proliferation and differentiation during the menstrual cycle and changes associated with endometrial bleeding disorders. *Microsc. Res. Techni.* 60, 412–419.
18. Khan, K.N., Kitajima, M., Hiraki, K., Fujishita, A., Sekine, I., Ishimaru, T., Masuzaki, H., 2010. Changes in tissue inflammation, angiogenesis and apoptosis in endometriosis, adenomyosis and uterine myoma after GnRH agonist therapy. *Hum. Reprod.* 25, 642–653.
19. Celik O, Hascalik S, Elter K, Tagluk ME, Gurates B, Aydin NE. Combating endometriosis by blocking proteasome and nuclear factor-kappaB pathways. *Hum Reprod.* 2008 Nov;23(11):2458-65. Epub 2008 Aug 2. PubMed PMID: 18676981.
20. Lee B, Du H, Taylor HS. Experimental murine endometriosis induces DNA methylation and altered gene expression in eutopic endometrium. *Biol Reprod* 2009;80:79–85
21. 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.
22. Kim JJ, Taylor HS, Lu Z, Ladhani O, Hastings JM, Jackson KS, Wu Y, Guo SW, Fazleabas AT. Altered expression of HOXA10 in endometriosis: potential role in decidualization. *Mol Hum Reprod* 2007;13:323–332.
23. Troy PJ, Daftary GS, Bagot CN, Taylor HS. Transcriptional repression of peri-implantation EMX2 expression in mammalian reproduction by HOXA10. *Mol Cell Biol* 2003;23:1–13.
24. Daftary GS, Taylor HS. EMX2 gene expression in the female reproductive tract and aberrant expression in the endometrium of patients with endometriosis. *J Clin Endocrinol Metab* 2004;89:2390–2396.
25. Kao, L.C., Germeyer, A., Tulac, S., Lobo, S., Yang, J.P., Taylor, R.N., Osteen, K., Lessey, B.A., Giudice, L.C., 2003. Expression profiling of endometrium from women with endometriosis reveals candidate genes for disease-based implantation failure and infertility. *Endocrinology* 144, 2870–2881.
26. Tiberi, F., Tropea, A., Apa, R., Romani, F., Lanzone, A., Marana, R., 2010a. Prokineticin 1 mRNA expression in

- the endometrium of healthy women and in the eutopic endometrium of women with endometriosis. *Fertil. Steril.* 93, 2145–2149.
27. Evans, J., Catalano, R.D., Brown, P., Sherwin, R., Critchley, H.O.D., Fazleabas, A.T., Jabbour, H.N., 2009. Prokineticin 1 mediates fetal-maternal dialogue regulating endometrial leukemia inhibitory factor. *FASEB J.* 23, 2165–2175.
 28. Cakmak H, Taylor HS. Implantation failure: molecular mechanisms and clinical treatment. *Hum Reprod Update.* 2011 Mar-Apr;17(2):242-53. Epub 2010 Aug 21. Review.
 29. Surrey, E.S., Lietz, A.K., Gustofson, R.L., Minjarez, D.A., Schoolcraft, W.B., 2010. Does endometrial integrin expression in endometriosis patients predict enhanced in vitro fertilization cycle outcomes after prolonged GnRH agonist therapy? *Fertil. Steril.* 93, 646–651.
 30. Murphy, A.A., Green, W.R., Bobbie, D., de la Cruz, Z.C., Rock, J.A., 1986. Unsuspected endometriosis documented by scanning electron microscopy in visually normal peritoneum. *Fertil. Steril.* 46, 522–524.
 31. Brosens, I., Vasquez, G., Gordts, S., 1984. Scanning electron microscopy study of the pelvic peritoneum in unexplained infertility and endometriosis. *Fertil. Steril.* 41, 21S.
 32. Benagiano, G., Brosens, I., 2011. Adenomyosis and endometriosis have a common origin. *J. Obstet. Gynecol. India* 61 (2), 146–152.
 33. Stoikos, C.J., Salamonson, L.A., Hannan, N.J., O'Connor, A.E., Rombauts, L., Dimitriadis, E., 2010. Activin A regulates trophoblast cell adhesive properties: implications for implantation failure in women with endometriosis-associated infertility. *Hum. Reprod.* 25, 1767–1774.
 34. Bulun, S.E., Yang, S., Fang, Z., Gurates, B., Tamura, M., Zhou, J., Sebastian, S., 2001. Role of aromatase in endometrial disease. *J. Steroid Biochem. Mol. Biol.* 79, 19–25.
 35. Bulun, S.E., Yang, S., Fang, Z., Gurates, B., Tamura, M., Sebastian, S., 2002. Estrogen production and metabolism in endometriosis. *Ann. N. Y. Acad. Sci.* 955, 75–85.
 36. Colette, S., Lousse, J.C., Defre`re, S., Curaba, M., Heilier, J.F., Van Langendonck, A., Mestdagt, M., Foidart, J.M., Loumaye, E., Donnez, J., 2009. Absence of aromatase protein and mRNA expression in endometriosis. *Hum. Reprod.* 24, 2133–2141.
 37. Simsek Y, Celik O, Karaer A, Gul M, Yilmaz E, Koc O, Colak C, Zengin S, Aydin NE. Therapeutic efficiency of Atosiban, an oxytocin receptor blocking agent in the treatment of experimental endometriosis. *Arch Gynecol Obstet.* 2012 Sep;286(3):777-83.
 38. Celik O, Hascalik S, Tagluk ME, Elter K, Parlakpinar H, Acet A. Assessment of myoelectrical signal parameters in estrogen, progesterone, and human chorionic gonadotropin administered in nonpregnant rat myometrium after ovariectomy. *Fertil Steril.* 2008 Jan;89(1):188-98.
 39. Brosens, J., Verhoeven, H., Campo, R., Gianaroli, L., Gordts, S., Hazekamp, J., Hagglund, L., Mardesic, T., Varila, E., Zech, J., Brosens, I., 2004. High endometrial aromatase P450 mRNA expression is associated with poor IVF outcome. *Hum. Reprod.* 19, 352–356.
 40. Dheenadayalu, K., Mak, I., Gordts, S., Campo, R., Higham, J., Puttemans, P., White, J., Christian, M., Fusi, L., Brosens, J., 2002. Aromatase P450 messenger RNA expression in eutopic endometrium is not a specific marker for pelvic endometriosis. *Fertil. Steril.* 78, 825–829.
 41. Purohit, A., Fusi, L., Brosens, J., Woo, L.W.L., Potter, B.V.L., Reed, M.J., 2008. Inhibition of steroid sulphatase activity in endometriotic implants by 667 COUMATE: A potential new therapy. *Hum. Reprod.* 23, 290–297.
 42. Colette, S., Lousse, J.C., Defre`re, S., Curaba, M., Heilier, J.F., Van Langendonck, A., Mestdagt, M., Foidart, J.M., Loumaye, E., Donnez, J., 2009. Absence of aromatase protein and mRNA expression in endometriosis. *Hum. Reprod.* 24, 2133–2141.
 43. Aghajanova, L., Tatsumi, K., Horcajadas, J.A., Zamah, A.M., Esteban, F.J., Herndon, C.N., Conti, M., Giudice, L.C., 2010. The protein kinase A pathway-regulated transcriptome of endometrial stromal fibroblasts reveals compromised differentiation and persistent proliferative potential in endometriosis. *Endocrinology* 151, 1341–1355.
 44. Kao, L.C., Germeyer, A., Tulac, S., Lobo, S., Yang, J.P., Taylor, R.N., Osteen, K., Lessey, B.A., Giudice, L.C., 2003. Expression profiling of endometrium from women with endometriosis reveals candidate genes for disease-based implantation failure and infertility. *Endocrinology* 144, 2870–2881.
 45. Burney, R.O., Talbi, S., Hamilton, A.E., Vo, K.C., Nyegaard, M., Nezhat, C.R., Lessey, B.A., Giudice, L.C., 2007. Gene expression analysis of endometrium reveals progesterone resistance and candidate susceptibility genes in women with endometriosis. *Endocrinology* 148, 3814–3826.
 46. Koninckx, P.R., Brosens, I.A., 1982. Clinical significance of the luteinized unruptured follicle syndrome as a cause of infertility. *Eur. J. Obstet. Gynecol. Reprod. Biol.* 13, 355–368.
 47. Attia, G.R., Zeitoun, K., Edwards, D., Johns, A., Carr, B.R., Bulun, S.E., 2000. Progesterone receptor isoform A but not B is expressed in endometriosis. *J. Clin. Endocrinol. Metab.* 85, 2897–2902.
 48. Aghajanova, L., Velarde, M.C., Giudice, L.C., 2009. The progesterone receptor coactivator Hic-5 is involved in the pathophysiology of endometriosis. *Endocrinology* 150, 3863–3870.
 49. Tranguch, S., Wang, H., Daikoku, T., Xie, H., Smith, D.F., Dey, S.K., 2007. FKBP52 deficiency-conferred uterine progesterone resistance is genetic background and pregnancy stage specific. *J. Clin. Invest.* 117, 1824–1834.
 50. Takano, M., et al, 2007. Transcriptional cross talk between the forkhead transcription factor forkhead box O1A and the progesterone receptor coordinates cell cycle regulation and differentiation in human endometrial stromal cells. *Mol. Endocrinol.* 21, 2334–2349.

51. Agarwal, A., Gupta, S., Sekhon, L., Shah, R., 2008. Redox considerations in female reproductive function and assisted reproduction: from molecular mechanisms to health implications. *Antioxid. Redox Signal* 10, 1375–1403.
52. Aghajanova, L., et al, 2011. Unique transcriptome, pathways, and networks in the human endometrial fibroblast response to progesterone in endometriosis. *Biol. Reprod.* 84, 801–815.
53. Klemmt, P.A., et al, 2006. Stromal cells from endometriotic lesions and endometrium from women with endometriosis have reduced decidualization capacity. *Fertil. Steril.* 85, 564–572.
54. Giudice, L.C., 2006. Endometrium in PCOS: implantation and predisposition to endocrine CA. *Best Practice Res.: Clin. Endocrinol. Metab.* 20, 235–244.
55. Pietro G Signorile et al, New evidence of the presence of endometriosis in the human fetus. *Reproductive BioMedicine Online* (2010) 21, 142-147.
56. Catherine Menier et al. The HLA-G non classical MHC class I molecule is expressed in cancer with poor prognosis. Implications in tumour escape from immune system and clinical applications, *Atlas of Genetics and Cytogenetics in Oncology and Haematology*, 2008. (<http://atlasgeneticsoncology.org>)
57. Nadja Tariverdian & Theoharis C. Theoharides et al. Neuroendocrine-immune disequilibrium and endometriosis: an interdisciplinary approach. *Semin Immunopathol* (2007) 29:193–210