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REVIEW ARTICLE

# Arrays to detect Erring Factors of Endometrial Origin in Endometriosis

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## ABSTRACT

Endometriosis is an estrogen-regulated chronic inflammatory disease, characterized by the presence and growth of endometrium-like tissue in extrauterine locations. Its prevalence is 6 to 10% of women in the general population, and 35 to 40% of women with pain and/or infertility. Endometriosis is manifested in different forms, of which peritoneal endometriosis, rectovaginal endometriosis and ovarian endometriosis are most common. Several investigations have been conducted to investigate the genetic basis of endometriosis. However, these studies have been unsuccessful in identifying robust genetic variants associated with endometriosis. On the contrary, the advent of whole genome cDNA microarray approach has allowed for the identification of genes that display modulation in their expression in an endometriotic tissue. Several biological pathways involved in the pathogenesis of endometriosis have been identified. This review article compiles the inferences drawn from high throughput investigations of endometriotic tissue.


**Keywords:** Endometriosis, Eutopic, Ectopic, Microarray.

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## INTRODUCTION

Endometriosis is an estrogen-dependent benign gynecological disease, characterized by the presence and growth of endometrial tissue (glands and stroma) in the extrauterine (ectopic) locations.[1,2] It is a chronic inflammatory disease occurring in 6 to 10% of women in the general population and in 35 to 40% of women with pain and/or infertility.[3,4] There are three clinically distinct endometriotic lesions, peritoneal implants that occur on the peritoneum, endometriomas that are cystic lesions sited in the ovary surrounded by endometrioid glands and rectovaginal nodules comprising fibrotic and endometriotic tissue that grow in the rectovaginal space.[5,6] The etiology of endometriosis remains unclear. Retrograde menstruation is considered as one of the etiological factors contributing to endometriosis.[5,7] However, retrograde menstruation occurs in 90% of women in the reproductive age, only 10% develop endometriosis.[8] Plausible explanations for the occurrence of the disease in only some women could be increased exposure to menstrual debris (e.g. increased menstrual flow, shorter cycle length), abnormal eutopic endometrium, altered peritoneal environment, reduced immune surveillance, and enhanced angiogenic potential.[9] There are other theories proposed to explain the origin of endometriosis. The coelomic metaplasia theory postulates that specialized cells transdifferentiate or transform into endometrial cells giving rise to endometriosis.[10] The induction theory proposes that the undifferentiated mesenchymal cells under the influence of factors secreted by the refluxed degenerated endometrium differentiate into endometrial epithelium and endometrium-like glands.[11] Another theory attributes the origin of endometriosis to the stem cells in the endometrium. The basal is layer of the endometrium, which is not shed during menstruation, is thought to be the source of stem cells.[12] Recently, cells representing the stem cell population in the human endometrium have been identified and proposed to be involved in the generation of ectopic endometrial lesions.[13] Owing to the fact that endometriosis is a multifactorial and polygenic disease, several, if not all, of these factors may play a role in the pathogenesis of endometriosis.

Gene mapping methodologies have been used to identify the genetic factors contributing to the pathogenesis of endometriosis.[14,15] The candidate genes chosen for these studies were based on biological mechanisms believed to be of relevance in the pathogenesis/pathophysiology of the disease. Some of the candidate genes known to be involved in detoxification pathways, sex steroid synthesis pathways and cytokine signaling pathways, adhesion molecules and matrix enzymes, and cell cycle regulation were analyzed.[16] Reports from these studies

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indicated the association of 76 genes with endometriosis susceptibility. Further, this information was used for linkage mapping analysis to search for genomic regions harboring genetic risk factors for endometriosis. One such large linkage study by Treloar et al combined Australian and British families and genotyped 4,985 women, including 2,709 with endometriosis.[17] The study reported two loci of significant linkage on chromosome 10q26 and another region of suggestive linkage on chromosome 20p13. Although chromosome 10q26 had been implicated in a candidate gene study[18] that reported aberrant endometrial EMX2 expression in women with endometriosis, variants of EMX2 have not been confirmed to contribute to the development of endometriosis.[19] Therefore, although promising, linkage analysis has yielded few significant genetic markers.[20] Due to the unsuccessful attempts in identification of susceptibility genes for endometriosis, efforts were made to identify the gene(s) involved by utilizing hypothesis-free fine mapping association methods or genome-wide association (GWA) methods using very densely spaced SNPs.[21] The methodology examines variation across the genome using computational models for comparison of the genotypes of people with and without disease to identify SNPs associated with disease.[22] Some of the commonly reported endometriosis candidate genes from association studies are glutathione S-transferase 1, estrogen receptor-α, progesterone receptor, TNF-α, IL-6, IL-10, tumor suppressor p53, vascular endothelial growth factor alpha (VEGFA), hydroxysteroid 17-β dehydrogenase 1, etc.[17,23,24] Despite these findings, to date, candidate gene studies have been unsuccessful in providing robust genetic variants associated with endometriosis. Both theoretical and empirical evidences suggest many genes or variants with small effects as risk factors.

## GENE EXPRESSION STUDIES: cDNA MICROARRAYS

Several studies have been undertaken using the cDNA microarray approach in an attempt to elucidate the mechanisms involved in the pathogenesis of endometriosis. However, the data obtained from these studies are incomplete owing to usage of chips containing limited number of human cDNAs.[25] Hence, came the advent of using a whole genome cDNA microarray approach to address this issue. The main advantage of using a whole-genome cDNA microarray approach is that it allows identification of families or pathways of genes that change in concert in a disease state rather than the 'hit or miss' approach inherent in the microarrays that contain only a fraction of the genome. Previously, Eyster et al used a microarray platform that contained approximately 3000 human genes to compare gene expression in ectopic *vs* eutopic endometrium of women with endometriosis. In another study, Eyster et al (2007) screened for 53000 human genes/transcribed sequences for analysis of paired eutopic and ectopic endometrium from the same patients.[26]

cDNA microarray analysis was also found useful for validation of animal model for human endometriosis.[27] Using cDNA microarray technology compared gene expression patterns of ectopic and normal endometrium in a rat model for intestinal endometriosis.[28] Four implants of the uterine horn measuring (2 × 2 mm) were sutured next to the mesenteric vessels of the small intestine in the experimental animals; while in the control animals, four silk sutures without the implants were attached to the mesentery of the intestine. All the animals were sacrificed 60 days postautotransplantation. A total of 168 genes (123 upregulated genes and 45 downregulated) were found to be differentially expressed in ectopic endometrium. Significantly, enriched gene ontology categories were identified. Of these, in particular, genes involved in immune response, inflammatory, chemotaxis, angiogenesis, response to wounding, programmed cell death, metallopeptidase function, cell adhesion, extracellular matrix and collagen metabolism were enriched significantly while downregulated genes were involved in processes like tube development, regulation of ossification and G1/S phase transition of mitotic cell cycle reached statistical significance. These data was found to be comparable with that reported for human disease.[29-31]

Attempts were made to investigate and characterize the biochemical changes that accompany early stages of development of endometriosis. In one such study, using a mouse model of endometriosis, the peritoneum excluding the transplant was sampled 24, 48 and 96 hours postautotransplantation of endometrium and subjected to microarray analysis. Since, endometriosis is known to be an extrauterine condition, the molecular profiling of the peritoneum may provide answers to a higher proportion of women developing peritoneal and ovarian endometriosis[32] as opposed to the rare cases of thoracic endometriosis,[33] colorectal obstructive endometriosis, etc.[34] Results from their data demonstrated an upregulation of adhesion molecules and genes involved in inflammatory response implying the significance of these during the early stages of endometriosis progression.[35]

### Eutopic Endometrium of Women with Endometriosis behaves Differently

Investigations have been carried out to examine the potential role of eutopic endometrium in the pathogenesis of endometriosis. In fact, there is growing evidence that eutopic endometrium of patients with endometriosis may

be different from that of women without endometriosis.[30] Matsuzakiet at al compared eutopic endometrium of women with deep endometriosis was compared with that of women without endometriosis across late proliferative, early-, mid- and late-secretory phases of menstrual cycle.[31] Several genes involved in two important signaling pathways: RAS/RAF/MAPK and PI3K, such as RON, SOS, 14-3-3 protein eta and uPAR in epithelial cells and KSR and PI3kp85 regulatory subunit alpha in stromal cells were found differentially expressed. Although, several of genes were found to be differentially expressed following cycle-phase matched comparison, these differences were not consistent across different patients with endometriosis when compared with women without endometriosis. The authors defended their data by proposing that the eutopic endometrium may be different among patients presenting different forms of endometriosis.[36]

However, there is an exception to this observation. Sharpe-Timms et al reported no significant differences in gene expression of eutopic endometrium of controls *vs* that of patients with endometriosis.[37] These contrasting observations could be attributable to differences in the study design and/or the methodology used in different studies.[38]

### Analysis of Paired Eutopic and Ectopic Endometrium of Women with Endometriosis

The gene expression profiles of paired eutopic and ectopic endometrium of women with endometriosis have been compared. Several genes were found to be differentially expressed between paired eutopic and ectopic endometrium of women with endometriosis. Eyster et al reported differential expression of eight genes namely β-actin, α-2 actin, vimentin, 40S ribosomal protein S23, Ig-λ light chain, Ig germ line H chain G-E-A region γ-2 constant region gene, major histocompatibility complex class 1, C and complement component 1S subcomponent in endometriosis implants compared with uterine endometrium.[29] Out of the eight genes that were differentially expressed, six were unique to the endometrium, with β-actin and α-2 actin genes common to other tissues (lung, placenta and uterus) as well. Ectopic endometrium is considered as an invasive tissue requiring cytoskeleton rearrangement that facilitates cell attachment and movement. It is known that vimentin and some forms of actin form cytoskeleton links.[39] This probably explains the upregulation of β-actin, α-2 actin and vimentin expression in endometriosis implants. Also, vimentin has been shown to have an indirect role in steroidogenesis. The lipid droplets containing cholesterol are connected with the cytoskeleton via vimentin,[40] allowing increased recruitment of these droplets by mitochondria during higher need of ectopic endometrium for estrogen synthesis. Although ribosomal proteins are generally considered being housekeeping genes, their expression has also been found to be regulated by estrogen.[41] Increased estrogen synthesis implies differential expression of estrogen-regulated genes and, therefore, an increased need for translation machinery. This justifies the upregulation of 40S ribosomal protein S23 in endometriosis implants compared to eutopic endometrium. Dysfunction of immune system has also been implicated in the etiology of endometriosis.[42] Upregulation of immune-related genes like Ig-λ light chain, Ig germ line H chain G-E-A region γ-2 constant region gene, major histocompatibility complex class 1, C and complement component 1S subcomponent in ectopic endometrium further supports the role of immune system in the development of endometriosis.

Khan et al compared paired eutopic and ectopic endometrium of 18 fertile women with ovarian endometriosis for genome-wide expression profiles.[43] Of the many genes, around 75 and 50% of expressed genes showed marked signals in autologous eutopic and ectopic samples, respectively. Genes that were differentially expressed by three-fold among different categories of comparison were used for generation of differential expression (DE) patterns. These DE patterns were used to highlight the enriched categories of pathways that could be involved in the pathogenesis of ovarian endometriosis. Among the enriched pathways, several signaling pathways involved in immune responses were commonly affected in eutopic and ectopic endometrium of women with endometriosis. Other than these, pathways related to cellular signaling, apoptosis and survival, cytoskeleton remodeling, chemotaxis, cell adhesion and several neurophysiological processes were also affected in accordance with several reports based on different experimental models.[44-46] Collectively, these studies indicate that eutopic endometrium which is transcriptionally dysfunctional in mediating immune and endocrine responses may be vulnerable to a transformation into endometriotic lesions. Studies also indicate a risk for malignant transformation in endometriosis.[9,47]

Gene expression profiles of paired early proliferative phase eutopic and ectopic endometria of patients with endometriosis were compared in patients having ovarian as well as peritoneal endometrioma.[48] Using rapid subtractive hybridization (RaSH) method, a total of 291 genes were found to be differentially expressed, out of which 191 were upregulated and 100 were downregulated in lesions. Out of these, 17 have been reported

previously for their association with endometriosis. These include c-MYC, MMP3, IGFBP1, CTGF, and PAEP while 274 genes have not been known for their association with endometriosis. Also, when this data was compared with that obtained from comparative genome hybridization (CGH) studies in endometriotic lesions, an overlap of 36 upregulated genes and 16 downregulated genes with the regions of gain and loss of genomic material respectively was observed.[49] This further demonstrates the contribution of genomic alterations to the pathophysiology of endometriosis.

## Gene Expression Analyses: A Tool for Classification of Endometriosis

There are different types of endometriosis known and various theories of histogenesis have been proposed based upon the location of endometriotic lesion.[36] It is therefore important to identify factors associated with different forms of endometriosis and their role in the clinical outcome of the disease. Till date, few attempts have been made to classify endometriosis on the basis of their expression profiles. In one such attempt, Wu et al taking into account the menstrual phase and location of the lesion, identified differentially expressed 904 genes/ESTs in eutopic and ectopic endometrium of women with endometriosis.[50] These differentially expressed genes were found to be enriched in different pathways which include platelet-derived growth factor receptor α (PDGFRA), platelet-derived growth factor β (PDGF),[51] rapidly accelerated fibrosarcoma (RAF1), mitogen-activated protein kinase (MAPK6), DUSP5 (a member of the MAPK phosphatase family), PLA2G5 (a member of cytosolic phospholipase A2 family), MKNK1 and RPS6KA3 (a member of ribosomal S6 kinase 2), transforming growth factor beta-3 (TGFB3), RCA1 (a member of Cdo42/Rac family), AKT1,[52,53] HSPB2, GSTM1, GGTLA1, GSTP1, GSS and GPX4 (involved in glutathione metabolism),[54] SOD1, cytochrome C (involved in oxidative stress).[55] In all, over 100 genes with known functions involved in a total of 79 pathways, which include oxidative stress, focal adhesion, Wnt signaling and MAPK signaling, were identified. Results from this study were in agreement with the previously published studies. An unsupervised two-way hierarchical clustering for the obtained data led to the classification of endometriosis into two subtypes based on the location of the lesion. This classification suggested that the subtypes of endometriosis are associated with distinct biological characteristics depicted by their gene signatures and more of such expression-based classification studies should be performed in order to better define the molecular basis underlying the development of subtypes of endometriosis.

Matsuzaki et al on the basis of microarray data obtained for deep infiltrating endometriosis (DIE), selected 12 potential candidate genes in ovarian endometriosis (OE) and matched eutopic endometrium and examined their expression in epithelial and stromal cells.[56] A total of 12 patients, 6 during proliferative phase and 6 during secretory phase of menstrual cycle were recruited for the study. Down regulation of $PGE_2$EP3 was detected in epithelial cells from both OE and DIE. It is known that endometriosis is an estrogen-dependent condition and so aberrant aromatase expression could be one of the factors contributing to the pathogenesis of endometriosis. Also, prostaglandin $E_2$ has been found to be a potent inducer of aromatase activity in endometriotic tissue while EP3 has been identified so far as the only inhibitory prostanoid receptor.[57] Therefore, downregulation of EP3 may favor growth of endometriotic tissue. There also exist differences in expression patterns of other genes, between OE and DIE. 17βHSD2 mRNA was detected in epithelial cells in all 12 samples of OE as opposed to absolute no detection in either epithelial or stromal cells from 50% of DIE cases. In contrast to their findings with DIE, significantly higher expression of COUP-TF2, an inhibitory transcription factor of aromatase, was detected in OE than in matched eutopic endometrium in the proliferative and secretory phases.[56,58] HSP90A, that actively participates in steroid-induced signal transduction,[59] was found to be upregulated in epithelial cells of endometriotic tissue. Few genes like PDGFRA and members of the downstream RAS/RAF/MAPK signaling pathway were differentially expressed between stromal cells from DIE and matched eutopic endometrium. These findings suggest that hormonal microenvironments, in association with aberrant expression of other genes, could influence the development of a particular form of endometriosis.

Zhao et al performed gene set enrichment analysis (GSEA) of six independent publicly available gene expression data sets to identify the common biological pathways involved in endometriosis.[60] Gene set enrichment analysis method identifies differences in expression between normal and patient samples.[61] Gene set enrichment analysis is likely to be a more powerful tool than conventional single-gene analysis in the study of complex diseases to investigate the subtle contribution of group of genes. Comparisons of the gene expression between lesion locations (ovarian *vs* peritoneal), phases of the uterine cycle (proliferative to midsecretory), and cell types (endometrial endothelial cells *vs* whole tissue) as well as overall eutopic *vs* ectopic endometrium were selected for the analyses. The transcriptomes of eutopic and ectopic endometrium suggested that ovarian endometriosis and peritoneal endometriosis are two different diseases.

## CONCLUSION

A deeper understanding into the pathogenesis of the disease can be achieved by focusing on deregulation of gene sets or pathways rather than on individual genes. Microarray is indeed an effective tool to study the differential expression of genes in biological tissues exposed to different microenvironments. Microarray based data have indicated differences in the gene expression profiles, depending upon the location of an ectopic endometrium. However, more such studies are needed in a larger sample size to deduce the specific role and interactions of the genes included in the related pathways. Such studies will expand our understanding of the etiology and pathogenesis of endometriosis and also will assist in the eventual development of novel treatments for endometriosis.

## REFERENCES


1. Guidice LC, Kao LC. Endometriosis. Lancet 2004 Nov; 364(9447):1789-1799.
2. Burney RO, Giudice L. Pathogenesis and pathophysiology of endometriosis. Fertil Steril 2012 Sept;98(3):511-519.
3. Eskenazi B, Warner ML. Epidemiology of endometriosis. Obstet Gynecol Clin North Am 1997 Jun;24(2):235-258.
4. Bulun SE. Endometriosis. N Engl J Med 2009 Jan;360(3): 268-279.
5. Gilabert-Estelles J, Braza-Boils A, Ramon LA, Zorio E, Medina P, Espana F, Estelles A. Role of microRNAs in gynecological pathology. Curr Med Chem 2012;19(15): 2406-2413.
6. Young VJ, Brown JK, Saunders PT, Horne AW. The role of the peritoneum in the pathogenesis of endometriosis. Hum Reprod Update 2013 Sep-Oct;19(5):558-569.
7. Cosin R, Gilabert- Estellas J, Ramon LA, España F, Gilabert J, Romeu A, Estellés A. Vascular endothelial growth factor polymorphisms (-460C/T, +405G/C and 936C/T) and endometriosis: their influence on vascular endothelial growth factor expression. Fertil Steril 2009 Oct;92(4):1214-1220.
8. Halme J, Hammond MG, Hulka JF, Raj SG, Talbert LM. Retrograde menstruation in healthy women and in patients with endometriosis. Obstet Gynecol 1984 Aug;64(2):151-155.
9. Varma R, Rollason T, Gupta JK, Maher ER. Endometriosis and neoplastic process. Reproduction 2004 Mar;127(3):293-304.
10. Gruenwald P. Origin of endometriosis from the mesenchyme of the celomic walls. Am J Obstet Gynecol 1942 Sep;44(3): 470-474.
11. Merrill JA. Endometrial induction of endometriosis across Millipore filters. Am J Obstet Gynecol 1966 Mar;94(6):780-790.
12. Padykula HA. Regeneration in the primate uterus: the role of stem cells. Ann N Y Acad Sci 1991;622:47-56.
13. Deane JA, Gualano RC, Gargett CE. Regenerating endometrium from stem/progenitor cells; is it abnormal in endometriosis, Asherman's syndrome and infertility? Curr Opin Obstet Gynecol 2013 Jun;25(3):193-200.
14. Stefansson H, Geirsson RT, Steinthorsdottir V, Jonsson H, Manolescu A, Kong A, Ingadottir G, Gulcher J, Stefansson K. Genetic factors contribute to the risk of developing endometriosis. Hum Reprod 2002 Mar;17(3):555-559.
15. Vigano P, Infantino M, Lattuada D, Lauletta R, Ponti E, Somigliana E, Vignali M, DiBlasio AM. Intercellular adhesion molecule-1 (ICAM-1) gene polymorphisms in endometriosis. Mol Hum Reprod 2003 Jan;9(1):47-52.
16. Falconer H, D' Hooghe T, Fried G. Endometriosis and genetic polymorphisms. Obstet Gynecol Surv 2007 Sep;62(9):616-628.
17. Treloar SA, Wicks J, Nyholt DR, Montgomery GW, Bahlo M, Smith V, Dawson G, Mackay IJ, Weeks DE, Bennett ST, et al. Genome wide linkage study in 1,176 affected sister pair families identifies a significant susceptibility locus for endometriosis on chromosome 10q26. Am J Hum Genet 2005 Sep;77(3):365-376.
18. 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 May;89(5):2390-2396.
19. Treloar SA, Zhao ZZ, Le L, Zondervan KT, Martin NG, Kennedy S, Nyholt DR, Montgomery GW. Variants in EMX2 and PTEN do not contribute to risk of endometriosis. Mol Hum Reprod 2007 Aug;13(8):587-594.
20. Kennedy S. Genetics of endometriosis: a review of the positional cloning approaches. Semin Reprod Med 2003 May; 21(2):111-118.
21. Montgomery GW, Nyholt DR, Zhao ZZ, Treloar SA, Painter JN, Missmer SA, Kennedy SH, Zondervan KT. The search for genes contributing to endometriosis risk. Hum Reprod Update 2008 Sep-Oct;14(5):447-457.
22. McCarthy MI, Hirschhorn JN. Genome-wide association studies: potential next steps on a genetic journey. Hum Mol Genet 2008 Oct;17(R2):R156-165.
23. Guo SW. Glutathione S-transferases M1/T1 gene polymorphisms and endometriosis: a meta-analysis of genetic association studies. Mol Hum Reprod 2005 Oct;11(10):729-743.
24. Huber A, Keck CC, Hefler LA, Schneeberger C, Huber JC, Bentz EK, Tempfer CB. Ten estrogen-related polymorphisms and endometriosis: a study of multiple gene-gene interactions. Obstet Gynecol 2005 Nov;106(5 Pt 1):1025-1031.
25. Zafrakas M, Tarlatzis BC, Streichert T, Pournaropoulos F, Wolfle U, Smeets SJ, WittekB, Grimbizis G, Brakenhoff RH, Pantel K, et al. Genome-wide microarray gene expression, array-CGH analysis, and telomerase activity in advanced ovarian endometriosis: a high degree of differentiation rather than malignant potential. Int J Mol Med 2008 Mar;21(3):335-344.
26. Eyster MK, Klinkova O, Kennedy V, Hansen K. Whole genome deoxyribonucleic acid micro array analysis of gene expression in ectopic versus eutopic endometrium. Fertil Steril 2007;88(6):1505-1533.
27. Flores I, Rivera E, Ruiz LA, Santiago OI, Vernon MW, Appleyard CB. Molecular profiling of experimental endometriosis identified gene expression patterns in common with human disease. Fertil Steril 2007 May;87(5):1180-1198.
28. Vernon MW, Wilson EA. Studies on the surgical induction of endometriosis in the rat. Fertil Steril 1985 Nov;44(5):684-694.
29. Eyster KM, Boles AL, Brannian JD, Hansen KA. DNA microarray analysis of gene expression markers of endometriosis. Fertil Steril 2002 Jan;77(1):38-42.
30. Kao LC, Germeyer A, Tulac S, Lobo S, Yang JP, Taylor RN, Osteen K, Lessey BA, Giudice LC. Expression profiling of endometrium from women with endometriosis reveals candidate genes for disease-based implantation failure and infertility. Endocrinol 2003 Jul;144(7):2870-2881.
31. Matsuzaki S, Canis M, Vaurs-Barrière C, Boespflug-Tanguy O, Dastugue B, Mage G. DNA microarray analysis of gene expression in eutopic endometrium from patients with deep

endometriosis using laser capture microdissection. Fertil Steril 2005 Oct;84(Suppl 2):1180-1190.
32. Dun EC, Taylor RN, Wieser F. Advances in the genetics of endometriosis. Genome Med 2010 Oct;2(10):75.
33. Rousset P, Rousset-Jablonski C, Alifano M, Mansuet-Lupo A, Buy JN, Revel MP. Thoracic endometriosis syndrome: CT and MRI features. Clin Radiol 2014 Mar;69(3):323-330.
34. Ono H, Honda S, Danjo Y, Nakamura K, Okabe M, Kimura T, Kawakami M, Nagashima K, Nishihara H. Rectal obstruction due to endometriosis: a case report and review of the Japanese literature. Int J Surg Case Rep 2014;5(11):845-848.
35. Umezawa M, Tanaka N, Tainaka H, Takeda K, Ihara T, Sugamata M. Microarray analysis provides insight into the early steps of pathophysiology of mouse endometriosis model induced by autotransplantation of endometrium. Life Sci 2009; 84(23-24):832-837.
36. 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): 585-596.
37. Sharpe-Timms KL. Endometrial anomalies in women with endometriosis. Ann NY Acad Sci 2001 Sep;943:131-147.
38. Thompson EB. The many roles of c-Myc in apoptosis. Annu Rev Physiol 1998;60:575-600.
39. Correia I, Chu D, Chou Y-H, Goldman RD, Matsudaira P. Integrating the actin and vimentin cytoskeletons: adhesion-dependent formation of fimbrin-vimentin complexes in macrophages. J Cell Biol 1999 Aug;146(4):831-842.
40. Hall PF. The roles of calmodulin, actin, and vimentin in steroid synthesis by adrenal cells. Steroids 1997 Jan;62(1):185-189.
41. Muller RE, Knowles JT. The synthesis of ribosomal RNA and ribosomal protein and their incorporation into ribosomes in the uterus of the oestrogen-stimulated immature rat. FEBS Lett 1984 Sep;174(2):253-257.
42. Giudice LC, Tazuke SI, Swiersz L. Status of current research on endometriosis. J Reprod Med 1998 Mar;43(Suppl 3):252-262.
43. Khan MA, Sengupta J, Mittal S, Ghosh D. Genome- wide expressions in autologous eutopic and ectopic endometrium of fertile women with endometriosis. Reprod Biol Endocrinol 2012;10:84.
44. Nasu K, Yuge A, Tsuno A, Nishida M, Narahara H. Involvement of resistance to apoptosis in the pathogenesis of endometriosis. Histol Histopathol 2009 Sep;24(9):1181-1192.
45. Gentilini D, Vigano P, Somigliana E, Vicentini LM, Vignali M, Busacca M, Di Blasio AM. Endometrial stromal cells from women with endometriosis reveal peculiar migratory behavior in response to ovarian steroids. Fertil Steril 2010 Feb;93(3):706-715.
46. Adachi M, Nasu K, Tsuno A, Kawano Y, Narahara H. Attachment to extracellular matrices is enhanced in human endometriotic stromal cells: a possible mechanism underlying the pathogenesis of endometriosis. Eur J Obstet Gynecol Reprod Biol 2011 Mar;155(1):85-88.
47. Vlahos NF, Economopoulos KP, Fotiou S. Endometriosis, in vitro fertilisation and the risk of gynaecological malignancies, including ovarian and breast cancer. Best Pract Res Clin Obstet Gynaecol 2010 Feb;24(1):39-50.
48. Meola J, Rosa E Silva JC, Dentillo DB, Da Silva WA Jr, Veiga-Castelli LC, Bernardes LA, Ferriani RA, de Paz CC, Giuliatti S, Martelli L. Differentially expressed genes in eutopic and ectopic endometrium of women with endometriosis. Fertil Steril 2010 Apr;93(6):1750-1773.
49. Gogusev J, Bouquet de Jolinière J, Telvi L, Doussau M, du Manoir S, Stojkoski A, Levardon M. Detection of DNA copy number changes in human endometriosis by comparative genomic hybridization. Hum Genet 1999 Nov;105(5):444-451.
50. Wu Y, Kajdacsy-Balla A, Strawn E, Basir Z, Halverson G, Jailwala P, Wang Y, Wang X, Ghosh S, Guo SW. Transcriptional characterizations of differences between eutopic and ectopic endometrium. Endocrinology transcriptional characterizations of differences between Eutopic and Ectopic Endometrium. Endocrinol 2006 Jan;147(1):232-246.
51. Munson L, Upadhyaya NB, Van Meter S. Platelet-derived growth factor promotes endometrial epithelial cell proliferation. Am J Obstet Gynecol 1995 Dec;173(6):1820-1825.
52. Ip YT, Davis RJ. Signal transduction by the c-Jun N-terminal kinase (JNK)—from inflammation to development. Curr Opin Cell Biol 1998 Apr;10(2):205-219.
53. Pi X, Yan C, Berk BC. Big mitogen-activated protein kinase (BMK1)/ERK5 protects endothelial cells from apoptosis. Circ Res 2004 Feb 20;94(3):362-369.
54. Ota H, Igarashi S, Kato N, Tanaka T. Aberrant expression of glutathione peroxidase in eutopic and ectopic endometrium in endometriosis and adenomyosis. Fertil Steril 2000 Aug; 74(2):313-318.
55. Ota H, Igarashi S, Hatazawa J, Tanaka T. Immunohistochemical assessment of superoxide dismutase expression in the endometrium in endometriosis and adenomyosis. Fertil Steril 1999 Jul;72(1):129-134.
56. Matsuzaki S, Canis M, Pouly JL, Botchorishvili R, Dechelotte P, Mage G. Differential expression of genes in eutopic and ectopic endometrium from patients with ovarian endometriosis. Fertil Steril 2006 Sep;86(3):548-553.
57. Noble LS, Takayama K, Zeitoun KM, Putman JM, Johns DA, Hinshelwood MM, Agarwal VR, Zhao Y, Carr BR, Bulun SE. Prostaglandin E2 stimulates aromatase expression in endometriosis-derived stromal cells. J Clin Endocrinol Metab 1997 Feb;82(2):600-606.
58. Zeitoun K, Takayama K, Michael MD, Bulun SE. Stimulation of aromatase P450 promoter (II) activity in endometriosis and its inhibition in endometrium are regulated by competitive binding of steroidogenic factor-1 and chicken ovalbumin upstream promoter transcription factor to the same cis-acting element. Mol Endocrinol 1999 Feb;13(2):239-253.
59. Segnitz B, Gehring U. The function of steroid hormone receptors is inhibited by the hsp90-specific compound geldanamycin. J Biol Chem 1997 Jul;272(30):18694-18701.
60. Zhao H, Wang Q, Bai C, He K, Pan Y. A cross-study gene set enrichment analysis identifies critical pathways in endometriosis. Reprod Biol Endocrinol 2009 Sep 8;7:94.
61. Mootha VK, Lindgren CM, Eriksson KF, Subramanian A, Sihag S, Lehar J, Puigserver P, Carlsson E, Ridderstråle M, Laurila E, et al. PGC-1alpha responsivegenes involved in oxidative phosphorylation are coordinately down regulated in human diabetes. Nat Genet 2003 Jul;34(3):267-273.