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Analysis of Differential Genes of Uyghur Women with Endometriosis in Xinjiang

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1. Introduction

Endometriosis (EM) is a common and important health problem, it is estimated to be present in 10%-15% of women in the reproductive age group and 25%-35% of infertile women. In the First Affiliated Hospital of Xinjiang Medical University in China, 447 cases primaily diagnosed with surgically confirmed endometriosis between January 2000 to September 2005, among them 349 cases of endometriosis were Han Chinese (78.1%) and 69 cases Uyghur women with endometriosis (15.3%).

Fig. 1.

Xinjiang is the biggest province of China inhabited by ethnic minorities in which Uyghur people are accounted for more than 40% of the total population. In recent years, the number of the Uyghur women with endometriosis have been increased in Xinjiang, however still clearly less than Han chinese with endometriosis. The data from pathology deparment of the First Affiliated Hospital of Xinjiang Medical University between 1992 and 1996 showed that there were only three Uyghur women with endometriosis (5.76%) among 52 cases. Between 2000 and 2001, only 4 Uyghur women with endometriosis (3.1%) among 128 patients. Between 2003 and 2010, there were 73 Uyghur women (13.45%) with endometriosis

in 565 cases. In Kashi, the Uyghur is occupied more than 80% of population. In the last 8 years, there were only 16 Uyghur women with endometriosis among 600 cases of endometriosis in People's Hospital of Kashi. It was demonstrated that the number of Uyghur women with endometriosis dramaticaly lower than Han chinese.

We performed At1asTMcDNA Expression Arrays (Clontech # 7854-1) cDNA microarray (containing 22,000. DNA)to compare the differential expression genes between ectopic endometrium of Uyghur and Han chinese women with endometriosis. Our study aimed to explore the molecular pathogenesis of endometriosis ethnic differences, so as to determine the cause of endometriosis of Uyghur women in Xinjiang.

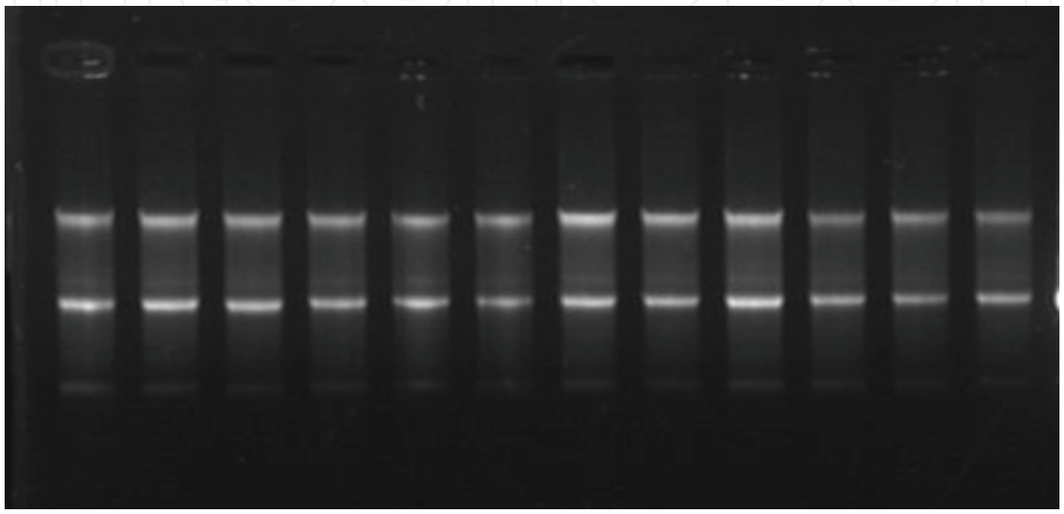

Fig. 2. Total RNA results.

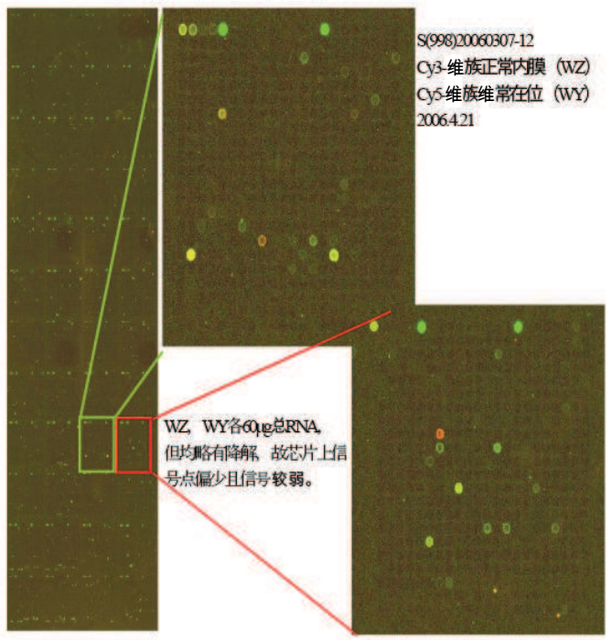

Fig. 3. Uyghur with and without endometriosis ectopic endometriosis hybrid.

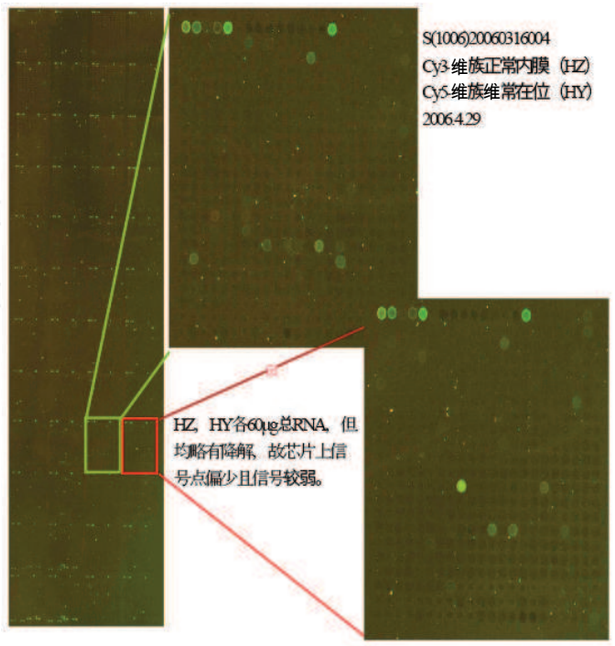

Fig. 4. Han with and without endometriosis ectopic endometriosis hybrid.

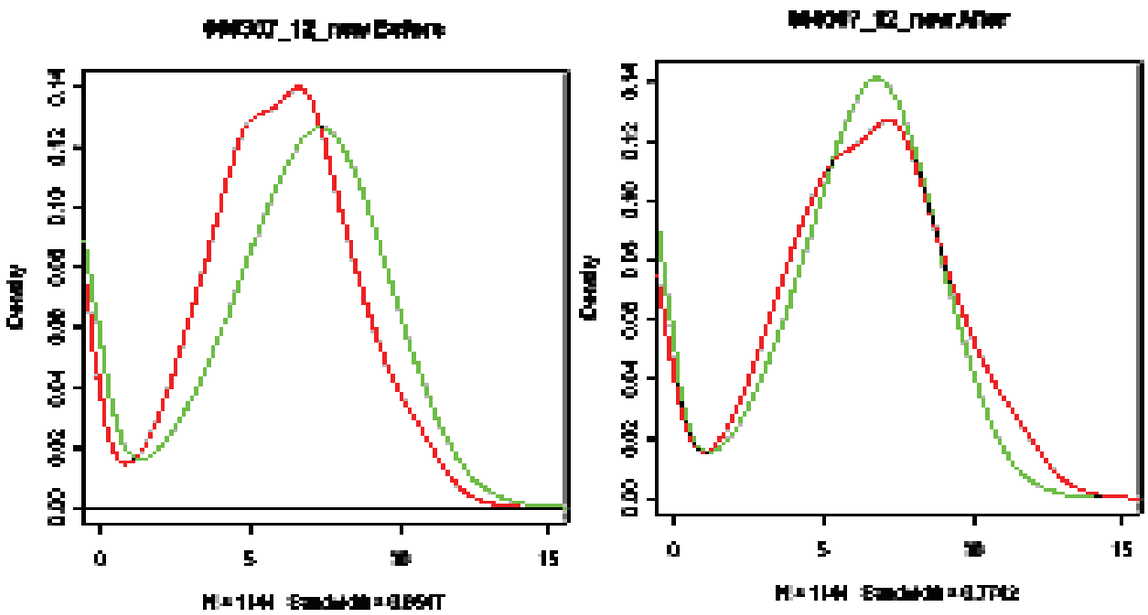

Fig. 5. Uyghur with and without endometriosis ectopic endometriosis hybrid before and after correction signal strength distribution.

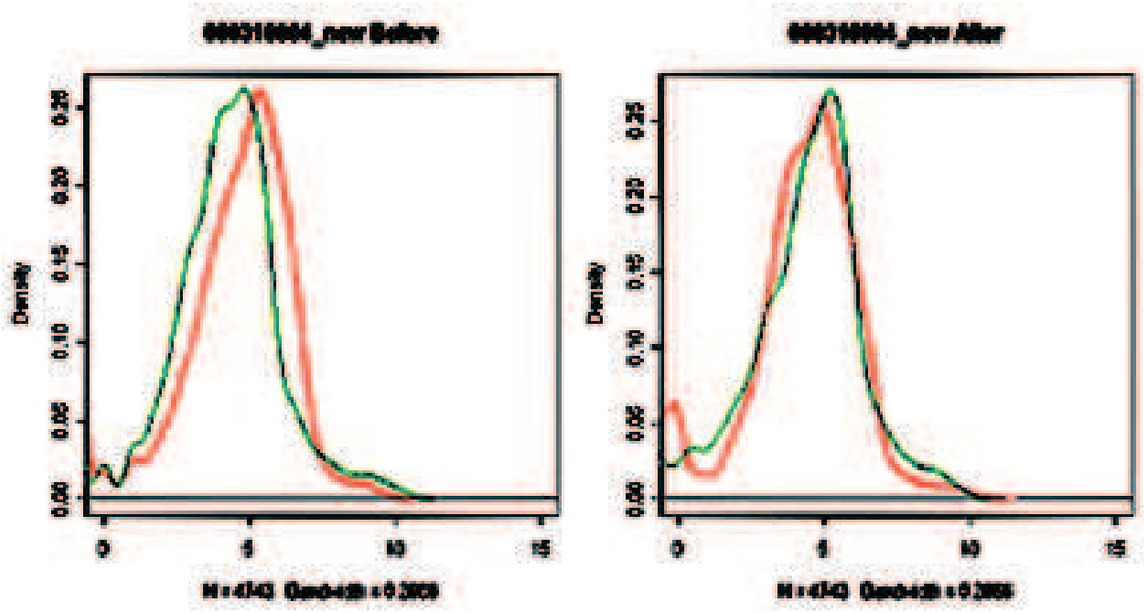

Fig. 6. Han with and without endometriosis ectopic endometriosis hybrid before and after correction signal strength distribution.

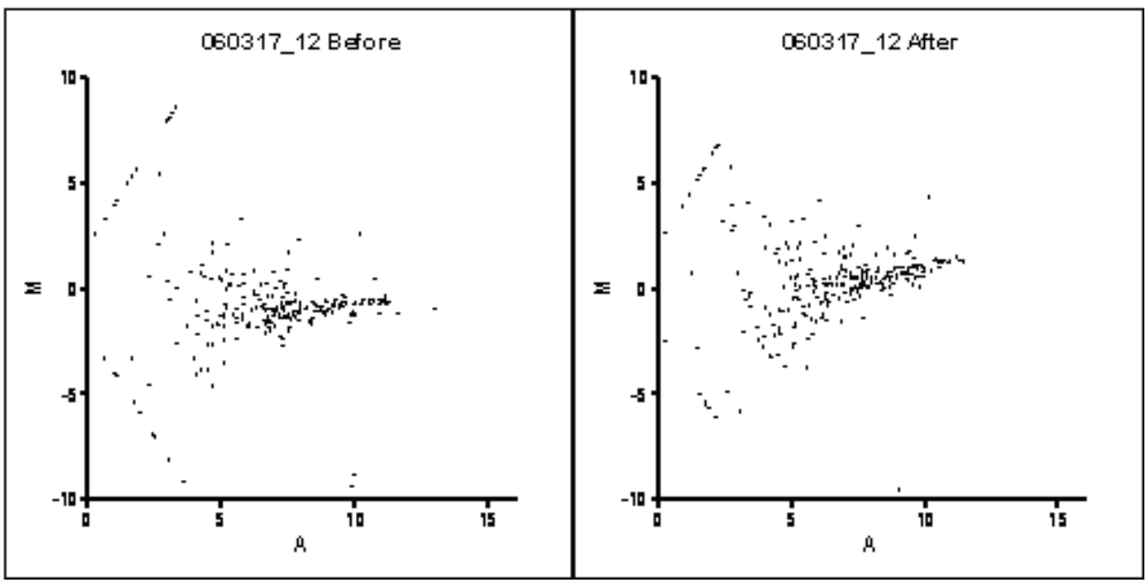

Fig. 7. Uyghur with and without endometriosis ectopic endometriosis hybrid before and after correction signal scatter.

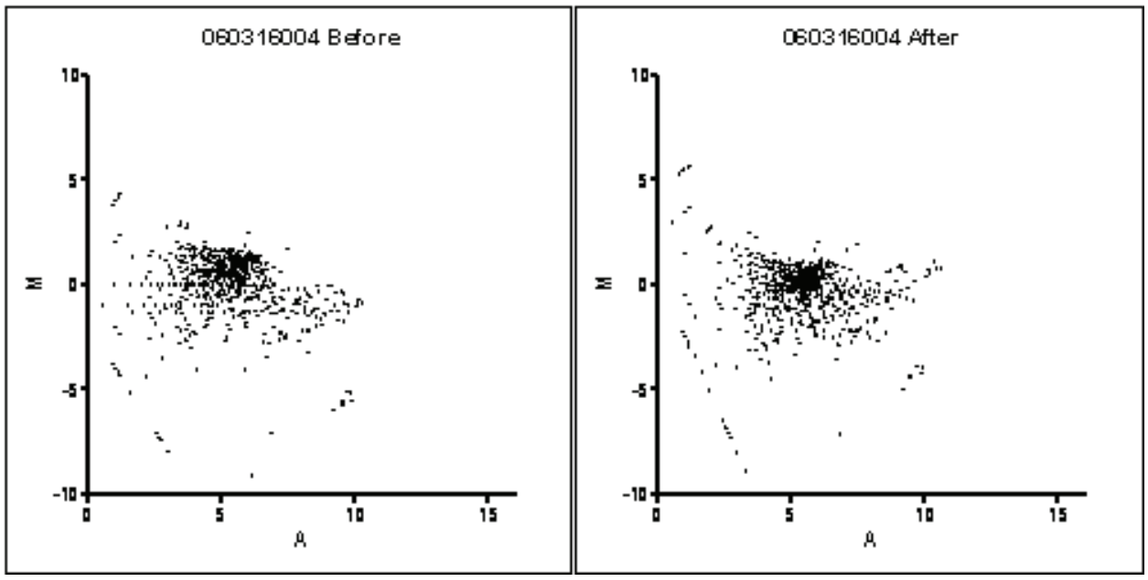

Fig. 8. Han with and without endometriosis ectopic endometriosis hybrid before and after correction signal scatter.

ID	Name	Cy5/Cy	Description
4340	FOS	3.649786	V-fos FBJ murine osteosarcoma viral oncogene homolog
7224	DCN	2.250099	Decorin
10599	VIM	1.629836	Vimentin
1900	GNG5	1.211619	Guanine nucleotide binding protein (G protein), gamma 5
1527	XCL1	1.169442	Small inducible cytokine subfamily C, mendometriosisber 1 (lymphotactin)
13167	IGFBP7	1.114798	Insulin-like growth factor binding protein 7
1651	RPS23	1.093641	Ribosomal protein S23
22665	TIMP3	-1.15294	Tissue inhibitor of metalloproteinase 3
13265	COL3A1	-1.55893	Collagen, type III, alpha 1 (Ehlers-Danlos syndrome type IV, autosomal dominant)
21389	RPL29	-1.63396	Ribosomal protein L29
8626	GAPD	-2.01536	Glyceraldehyde-3-phosphate dehydrogenase
22689	GAPD	-2.30404	Glyceraldehyde-3-phosphate dehydrogenase
22785	GAPD	-2.71698	Glyceraldehyde-3-phosphate dehydrogenase

Table 1. Uyghur with and without endometriosis ectopic endometriosis differential genes.

ID	Name	Rate of Cy5/Cy3	Description
18428	FTL	4.340706	ESTs, Weakly similar to FRHUL ferritin light chain [H.sapiens]
8586	APOE	3.768085	Apolipoprotein E
7998	CD74	3.623251	CD74 antigen (invariant polypeptide of major histocompatibility complex, class II antigen-associated
21034	CTSD	2.992721	Cathepsin D (lysosomal aspartyl protease)
20900	IGL@	2.941947	H.sapiens mRNA for IgG lambda light chain V-J-C region (clone Tgl9)
18699	BIN3	3.235432	Bridging integrator 3
10633	CTSB	2.736133	Cathepsin B
16743	IGKV1-9	2.482954	Immunoglobulin kappa variable 1-9
10901	IGHG3	2.24961	Immunoglobulin heavy constant gamma 3 (G3m marker)
17716	ZFHXI B	2.221742	Zinc finger homeobox 1 b
15732	ACTA2	1.939791	Actin, alpha 2, smooth muscle, aorta
6876	HLA-G	1.795164	HLA-G histocompatibility antigen, class I, G
9464	HLA-A	1.617767	Major histocompatibility complex, class I, A
12611	ITM2C	1.60875	Integral mendometriosisbrane protein 3
9202	DLGAP4	1.56221	KIAA0964 protein
6875	WNT7A	1.55996	Wingless-type MMTV integration site family, mendometriosisber 7A
6494	FTH1	1.55145	Ferritin, heavy polypeptide 1
6952	TMSB10	1.539032	Thymosin, beta 10
22794	ACTB	1.51553	Actin, beta
22769	ACTB	1.495315	Actin, beta
10474	FLJ14950	1.489821	Hypothetical protein FLJ14950
13167	IGFBP7	1.486395	Insulin-like growth factor binding protein 7
18071	HUMMHC W1A	1.460991	Cw1 antigen
22698	ACTB	1.45868	Actin, beta
12651	SPARC	1.441213	Secreted protein, acidic, cysteine-rich (osteonectin)
22696	RPL5	1.421712	Ribosomal protein L5
13180	LOC51237	1.416254	Hypothetical protein
14701	HSU79274	1.391079	Protein predicted by clone 23733
22793	ACTB	1.374773	Actin, beta
5712	GPX3	1.370492	Glutathione peroxidase 3(plasma)
22985	ACTB	1.342603	Actin, beta
22674	ACTB	1.333726	Actin, beta
22697	ACTB	1.33342	Actin, beta
21176	KPT13	1.327325	Keratin 13
22889	ACTB	1.325337	Actin, beta
22700	CYC1	1.325323	Cytochrome c-1
23193	LOC389643	1.323453	LOC389643

Table 2. Han with and without endometriosis ectopic endometriosis differential genes.

ID	Name	Rate of Cy5/Cy3	Description
9988	ACTB	1.293784	Actin, beta
20299	IL1 RN	1.283803	Interleukin 1 receptor antagonist
16687	TP73	1.277275	Tumor protein p73
22986	ACTB	1.267406	Actin, beta
22770	ACTB	1.258614	Actin, beta
10599	VIM	1.251847	Vimentin
22865	ACTB	1.233357	Actin, beta
22345	LOC440552	1.232367	similar to OK/SW-CL.16
8173	MARK2	1.227909	ELKL motif kinase
22962	ACTB	1.219306	Actin, beta
21216	SLPI	1.215856	Secretory leukocyte protease inhibitor
22690	ANKT	1.213863	Nucleolar protein
23200	LOC389622	1.212664	LOC389622
22961	ACTB	1.212137	Actin, beta
22673	ACTB	1.210056	Actin, beta
22890	ACTB	1.208872	Actin, beta
19718	SULT1C2	1.207869	Sulfotransferase family, cytosolic, 1C, mendometriosisber 2
12903	HSPA5BP1	1.179906	Hypothetical protein FLJ20539
22785	PDGFRA	1.159421	Platelet-derives growth factor receptor
1900	GNG5	1.125384	Guanine nucleotide binding protein (G protein), gamma 5
20231	SERF2	1.112907	Small EDRK-rich factor 2
15491	ZNF14	1.104864	Zinc finger protein 14 (KOX 6)
9735	KIAA0635	1.100348	Hypothetical protein FLJ13621
16540	CDW92	1.092801	CDw92 antigen
22762	COPEB	1.08944	Core promoterelendometriosisent binding protein
22866	ACTB	1.083347	Actin, beta
8626	GPX3	1.078504	Glutathione peroxidase 3(plasma)
1401	ELAVL3	1.077059	ELAV (endometriosisbryonic lethal, abnormal vision, Drosophila)-like 3 (Hu antigen C)
19581	GNG5	1.057676	Guanine nucleotide binding protein (G protein), gamma 5
7186	ID3	1.057184	Inhibitor of DNA binding 3, dominant negative helix-loop-helix protein
17362	FKBP14	1.036957	Hypothetical protein FLJ20731
9824	MTBP	1.030879	Mdm2, transformed 3T3 cell double minute 2, p53 binding protein (mouse) binding protein, 104kD
8364	ARHGDIA	1.029915	Rho GDP dissociation inhibitor (GDI) alpha
21961	RPS23	1.025033	Ribosomal protein S23
1580	NELF	1.017617	DKFZP586J1624 protein
22665	GAPD	-1.003765	Glyceraldehyde-3-phosphate dehydrogenase
22761	GAPD	-1.001544	Glyceraldehyde-3-phosphate dehydrogenase
17133	GAPD	-4.29046	Glyceraldehyde-3-phosphate dehydrogenase

Table 2. Han with and without endometriosis ectopic endometriosis differential genes. (Continuation)

ID	Name	Rate of Cy5/Cy3	Description
7979	PAEP	-5.57639	Progestagen-associated endometrial protein (placental protein 14, pregnancy-associated endometrial a
1813	TIMP3	-2.748361	Tissue inhibitor of metalloproteinase 3 (erythroid potentiating activity, collagenase inhibitor)

Table 2. Han with and without endometriosis ectopic endometriosis differential genes. (Continuation)

2. The incidence of endometriosis of Uyghur ethnic group in Xinjiang

The incidence of endometriosis has no precise information. Researchs have found that Asian women with endometriosis have a higher prevalence, and its disease risk :OR:8.6(95%CI ll.4—20.7). There was an exploratory study suggested that there might be an associated risk of endometriosis for those women who have worked as a flight attendant, service station attendant, or health worker, particularly a nurse. But they have not been reported the correlation between nationality, religion and other factors with endometriosis.

Clinical and epidemiological survey found that endometriosis has a genetic predisposition and significant family aggregation, and it loss of heterozygosity of 40% -70%. Dingyan(researcher in Xinjiang) found that no evidence was found to suggest an association between GSTM1-null genotype and endometriosis in the Hans chinese and Uyghurs. An association was found between GSTT1 -null genotype and endometriosis in the Hans chinese, but not in the Uyghurs. The two ethnic groups have different genetic predisposing factors to the development of endometriosis. There were significant difference in the frequencies of these two points among the Han chinese, European and Uyghur in Xinjiang. In Uyghur the distribution of CYP 1 A 1 /MspI genotypes were different from Han chinese and European.

3. The spectrum of microarray applications on endometriosis

A large number of microarray gene-specific cDNA are fixed on a glass or silica using the hybridization principles to detect the mRNA of the different sources. This study shows the different organization, different cells and tissues in different developmental stages that have differentially expressed genes. Development of molecular mechanisms provide theoretical basis for gene diagnosis and treatment of cutting-edge biotechnology. The theory proposed by Sampson in 1927 suggests that endometrial tissue is released into the peritoneal cavity via retrograde menstruation. The shed tissue then implants and grows ectopically. This theory is supported by the fact that up to 76% -90% of women experience retrograde menstruation ; and yet, endometriosis only affects 10% -15% of women. Reference to foreign literature, different individuals sample of patient with endometriosis geometric mixed, different individuals sample of patient without endometriosis geometric mixed, to eliminate non-specific genetic differences between individuals, and search for specific associated genes with endometriosis. By the gene microarray expression profiling 22,000 points compare ectopic endometrium and normal ectopic endometrial of the Uyghur and Han chinese with endometriosis, 11 differential genes expressed in ectopic endometrium were

screened out between Uyhgur women with or without endometriosis respectively, FOS, DCN, VIN, GNGS, XCL 1, IGFBP7, PRS23, TIMP3, COL3A1, PRL29, GAPD; GAPD expression in the three loci, including FOS, DCN, VIN, GNGS, XCL1, IGFBP7, PRS23 were up-regulated, and TIMP3, COL3A1, PRL29, GAPD were down-regulated. The Han chinese group were significantly different genes, 58 of which TIMP3, PAEP, GADP were down-regulated, but GADP expressed in three loci shows different range. And from a different CD74, ACTA2, GPX3 and other 55 genes were upregulated, ACTB appear in 17 loci, GNGS appear in two loci. The same genes difference between the two groups is VIM, GNGS, PRS23, GAPD, TIMP3, including GAPD, TIMP3 are down-regulated. We get different genes according to their main function and are divided into the following categories: immune-related genes,proto-oncogenes and tumor suppressor genes,cell receptor,ion channels and transport protein; cytoskeleton and sports-related protein, apoptosis-related protein; DNA synthesis and repair, recombinant protein, DNA binding, transcription and transcription factors,cell signaling and transmission white and some unknown functional genes.

4. The possible role of clinically relevant different gene in endometriosis pathogenesis

The difference in the screened genes, tissue inhibitor of metalloproteinase 3 (TIMP-3) both in the Han chinese and Uyghur with endometriosis were down-regulated. The study of Zhou Honghui found that TIMP-3 down-regulation is remarkable in the secretory phase than proliferative phase. TIMP is a metalloproteinase (MMPs) inhibitors by the endometrial cells of MMPs which plays an important role in the invasion of the peritoneum and other connective tissue. Increased endometrial MMPs and TIMP down-regulation with the development of endometriosis is closely related. Because of TIMP up-regulation and MMPs down-reglation, ectopic endometrial of endometriosis is more invasive than normal force, and develop to the peritoneal endometriotic lesions.Angiogenesis is considered as a major process in the pathogenesis of endometriosis. Many factors are involved in this complex mechanism, and the vascular endothelial growth factor (VEGF) is an important mediator of angiogenesis; it is a potent endothelial cell mitogen, morphogen, and vascular permeability-inducing agent. VEGF binds to either of two tyrosine kinase receptors, the fm5-like tyrosine kinase (flt) and the kinase domain receptor (KDR or Flk-1). Peritoneal endometriotic lesions with high proliferative activity are also accompanied by high angiogenic activity, as reflected by higher expression of VEGF-A in stroma and glandular epithelium and VEGFR-2 in blood vessels. In our recent study, we showed that the vascular density and the expression of VEGF and its receptor VEGFR-2 (Flk-1) are significantly higher in deeply infiltrating endometriosis affecting the ovary, bladder and mainly the rectosigmoid, compared with the ectopic endometrium.

Controlled clinical analyses of angiogenesis in human endometriotic lesions are limited, because it is not possible to monitor the lesions without repeated laparoscopies. Thus, research into the fundamental mechanisms by which menstrual endometrium adheres, invades and establishes a functional vasculature to persist in an ectopic site, as well as the development of new therapeutical approaches, is best performed in experimental animal models. In contrast to humans and non-human primates, estrous animals do not shed their endometrial tissue and therefore do not develop endometriosis spontaneously. However,

endometriosis can be induced by transplanting endometrial tissue to ectopic sites, and the establishment of an experimental model of endometriosis may be a good way to study the endometriosis angiogenesis process, and allow evaluation of the balance of the many factors involved.

This study by glyceraldehyde 3-phosphate dehydrogenase (GAPD) gene in Han chinese and Uyghurs with endometriosis group are down-regulated, GAPD genes are housekeeping gene family, Gene bank No. NM-002046, is a basic enzyme in the human body.It is a key enzyme of a series of biochemical reactions of the glycolysis, which generate ATP for the source of human cells energy, a variety of cells are present in the body, involved in glucose metabolism in glycolysis, in 12p13.

In Han and Uyghur groups the same set of common up-regulated genes are GNGS, VIM and PRS23. Abundance or localization changes in endometrial tissue were validated by immunohistochemistry and Western blotting. In addition, multiple charge and size isoforms were observed for VIM in endometriosis patients that was below the level of detection in healthy women.

Our experiment confirmed endometriosis may be related to multiple factors similar as diabetes, asthma, cancer-related disease, genetics and aberrant regulation in the endometrium and endometriotic. Lower different genes expression on Uyghur women with endometriosis compared to Han Chinese women with endometriosis may be the essential factor for relatively lower incidence of endometriosis on Uyghur women. Most genes we found on the endometrium of both Uyghur and Han Chinese women with endometriosis were the cytoskeleton, adhesion, invaded and immune related gene,patially explained the mechanism of malignant biological behaviors.

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This book provides an insight into the emerging trends in pathogenesis, diagnosis and management of endometriosis. Key features of the book include overviews of endometriosis; endometrial angiogenesis, stem cells involvement, immunological and hormonal aspects related to the disease pathogenesis; recent research reports on infertility, endometrial receptivity, ovarian cancer and altered gene expression associated with endometriosis; various predictive markers, and imaging modalities including MRI and ultrasound for efficient diagnosis; as well as current non-hormonal and hormonal treatment strategies This book is expected to be a valuable resource for clinicians, scientists and students who would like to have an improved understanding of endometriosis and also appreciate recent research trends associated with this disease.

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