Gene polymorphism involment in endometriosis

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Abstract

Endometriosis is a benign gynaecological disease with an unclear pathophysiology characterized by ectopic endometrium causing endometrium-like inflammatory lesions outside the uterine cavity. Genetic, endocrine, immunological, and environmental factors have been suggested in its pathogenesis. A great number of studies have investigated genetic polymorphisms as a possible factor contributing to the development of endometriosis, with a strikingly large amount of conflicting results. Most of the studies showed positive correlations between different polymorphisms and endometriosis. This relationship is most clearly seen in the case of pro-inflammatory and anti-inflammatory cytokines (interleukin (IL)-1, IL-6, IL-10, IL-18,tumor necrosis factor (TNF)-α, interferon-gamma), but also in the case of steroid-synthesizing enzymes and detoxifying enzymes and receptors, estradiol metabolism, growth factor systems, endothelial nitric oxide synthesis and adhesion molecules and matrix enzymes. On the other hand, a negative correlation between gene polymorphism and endometriosis seems to be present in relation to apoptosis, cell cycle and oncogenes. Moreover, some of the studied polymorphisms (TNF:g.[-1031T >C] and the TNF:g.[-863C >A], vascular endothelial growth factor (VEGF) +405 C/G) may be associated with advanced stage endometriosis or with the painful phenotype of endometriosis (IL-16 rs4778889 T/C). Contrary, some genes might be protective factors for endometriosis (rs699947 (A>C) and rs1570360 (G>A) polymorphism of the VEGF gene). In this review, we tried to summarize the most important data regarding the implication of genes with nucleotide polymorphisms in the pathogenesis of endometriosis, but future association studies may further illuminate the role of gene polymorphism in the pathogenesis of endometriosis.

Keywords: *cytokines, inflammation, gene polymorphism, endometriosis*

1.Introduction

Endometriosis is a frequent benign gynaecological disease which affects women of reproductive age, being able to cause pelvic pain and infertility. It is characterised by the implantation and growth of the endometrial tissue outside the uterine cavity, with a prevalence of approximately 10% in women of reproductive age and up to 30-50% of infertile women[1]. This is a chronic inflammatory disease with immune implications and at the same time with polygenic predisposition.

The pathogenesis of this disease is unclear, involving genetic, endocrine, immune and environmental factors. Several theories have been advanced in attempt to explain the pathogenesis of endometriosis. Recently, studies of genetic association emphasised correlations between developing endometriosis and certain genetic polymorphisms, even though the genes that are involved in the susceptibility of developing and progression of endometriosis are still unknown[2]. Family studies on endometriosis show a high risk of developing the disease for relatives of the women that are affected, which suggests the involvement of a genetic component. A number of 20 candidate genes in association with endometriosis have been identified by using a number of various techniques for analysing genetic polymorphisms[3].

We searched MEDLINE, EMBASE, Web of Science, and CBM databases for articles published between 1995 and 2014 which addressed an association of genetic polymorphisms with endometriosis.

This analysis aims at reviewing current data regarding different investigated genes, the techniques used and proof in favour of or against their involvement in the pathogenesis of endometriosis.

2. Specific genetic polymorphism

Inflammation

■ Pro-inflammatory and anti-inflammatory citokines (interleukin (IL)-1γ, IL-1R, IL-1Ra, IL-2, IL-2Rβ, IL-4, IL-6, IL-10, IL-16, IL-18, interferon (IFN)γ, tumor necrosis factor (TNF)-α, TNF-β, TNF-R2)

Several studies have reported that the inflammatory response and immunological factors play an important role in the pathogenesis of endometriosis. High levels of some pro-inflammatory cytokines, as IL-1, IL-6, IL-8 or TNFα1 have been observed in the case of women suffering from endometriosis[4].

Several members and regulatory components of the interleukin family have been examined for polymorphisms including IL-1β, IL-1R, IL-1Rα, IL-2, IL-2Rβ, IL-4, IL-6, IL-10, IL-16, IL-18, IFNγ.

Several studies have shown positive correlations between special polymorphic sites and endometriosis. Two studies groups have reported an association between the 1031T/C polymorphism of the TNFα promoter gene and the presence of endometriosis[5,6]. On the other hand, it has been demonstrated that the homozygote variant of TNF:g.-1031CC, could be associated with the advanced stages of endometriosis and

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that the homozygote variant of TNF:g.-863CC, has a protective role in the pathogenesis of endometriosis[7]. At the same time, a very recent meta-analysis shows that the same polymorphism, 1031 T/C, might act as a factor that reduces the risk of endometriosis, but the TNFα-238A/G and IL-6 -174C/G polymorphisms could act as risk factors for the development of the disease. The authors have not observed any association between the gene polymorphism TNFα-308A/G or IL-6 -634C/G and the presence of endometriosis[8].

Studies on ILβ1 (exon 5, promoter 511), IL-4 (-590 C/T) and IL-6 (-174 G/C) polymorphisms, have shown negative correlations with endometriosis in all cases. However, Wieser and contributors have reported a high prevalence of endometriosis in association with the IL-6 (-174 G) allele[9].

There seems to be a synergism between certain inflammatory factors that might be involved in endometriosis. Thus, Kitawaki et al. have observed that the IL-6 (-634 C/G) gene polymorphism and the gene polymorphism of intercellular adhesion molecule-1 469K/E affect in a synergic way the susceptibility to endometriosis in the case of Asian population[10].

Moreover, studies on the IFNγ polymorphism and on the IL-2 (-627 C) receptor have shown their association with endometriosis in case of Japanese and Taiwanese women. Seven alleles (12-18 repeats) have been discovered in relation to the gene polymorphism of IFNγ CA(n) repeat. It has been observed that endometriosis patients showed a significantly higher presence of the allelic variants composed of fewer repeats (12-13 repeats), thus suggesting that IFNγ CA(n) repeat might be associated with a high risk of developing endometriosis[11].

IL-10 is one of the main immune-regulating cytokines. The biological actions include mainly inhibiting effects as the inactivation of macrophages and inhibition of pro-inflammatory cytokines. Several single nucleotide polymorphisms (SNPs) of the promoter region of IL-10 have been described. A recent meta-analysis suggests that the IL-10 (-592 A/C) polymorphism assigns susceptibility to endometriosis, but associations between IL-10 (-1082 A/G and -892 T/C) and susceptibility to endometriosis have not been observed[12]. Nevertheless, it has also been observed that IL-10 ACC/ACC genotype is associated with the occurrence of endometriosis, this genotype being known as a 'low-producer' of IL-10[13].

Regarding the other interleukins, it has been shown that the gene polymorphism of IL-2Rβ (-C627T) is not associated with the advanced stages of endometriosis among Korean women, and further studies are necessary to explain a possible association between this and susceptibility to endometriosis[14]. On the other hand, a recent study has confirmed the association of the IL-16 (rs4778889T/C) gene polymorphism with a high risk of developing endometriosis, as well as with the painful phenotype of this disease[15]. Another study focussed on IL-18 has demonstrated the existence of a positive relation between the gene polymorphism of IL-18 (C607A homozygote type) and the risk of developing endometriosis or its stage[16].

In conclusion, certain specific polymorphisms of proinflammatory and anti-inflammatory cytokines can be associated with endometriosis. The most interesting genes to be studied are TNFα (-1031), IL-10 (-1082, -592, -627), IFNγ CA-repeat and IL-2R. To be noted is the fact that these associations have been observed mainly among Asian women and this data might not be relevant in the case of other ethnic groups.

Hormone Receptors

■ **Androgen receptor (AR), estrogen receptor (ER) and progesterone receptor (PR)**

Endometriosis, adenomyosis and leiomyoma usually appear in women of reproductive age, regress after menopause or ovariectomy and are generally considered to be estrogen-dependent. The induction a hypoestrogenic stage by using gonadotropin-releasing hormone agonists and gestagens is considered to be the gold-standard in medical treatment of endometriosis. Moreover, an increase of AR caused by estrogens is recommended as one of the biological phenomena in relation to the endometrial growth induced estrogenically. A genetic variation of AR has been associated with a high risk of developing endometriosis[17,18].

Progesterone is largely used in the treatment of endometriosis. Recent studies have shown that the modulation of the progesterone receptors with selective modulators of the progesterone receptors (SPRMs) can determine a reduction of the pain associated with endometriosis. Thus, SPRMs, beside their other medical uses, could have a therapeutic potential in treating endometriosis[19].

Hsieh et al. have concluded that the gene polymorphism of AR could contribute to the pathogenesis of endometriosis[20], while Lattuada et al. have reached the opposite conclusion[21].

Georgiou et al have explored the association between the polymorphism of the ER-2 allele, the multi-allele polymorphism (microsatellite) and endometriosis. A statistically significant difference has been observed in the frequency of allele Pvu II polymorphism as well as in the multi-allele (TA)n polymorphism. It has been concluded that the gene variability of ER might contribute to the pathogenesis of endometriosis[22].

The functional characterization of the mutations of the ERα gene has shown that two ERα mutant proteins present a sever limitation of deoxyribonucleic acid (DNA) binding and of trans-activating properties, secondary to an altered reaction to estrogen or to changes in the epidermal growth factor (EGF) activation. Thus, it has been suggested that ER mutations/polymorphisms might make endometriosis cells resistant to hypoestrogenic conditions, and as a consequence causing the failure of the estrogen oblation therapy[23].

Another recent study has concluded that the polymorphism of progesterone receptor promoter (-331 G/A) might modify the epidemiologic molecular path,

which includes not only the occurrence of endometriosis, but also its subsequent transformation into endometrioid/clear cells ovarian cancer[24].

In conclusion, ERα gene polymorphism might be involved in the pathogenesis of endometriosis, while the PR and AR polymorphisms might have a lower association with endometriosis.

Angiogenesis and Growth Factor Systems

■ **EGFR Receptor (EGFR), Transforming-β-Receptor 1 (TβR-I), and Vascular Endothelial Growth Factor (VEGF)**

These systems are involved in the growth, differentiation and vascularisation of normal and tumour cells. The EGFR activation determines effects which include DNA synthesis and cellular differentiation, the normal expression of EGFR being involved in the pathogenesis of various diseases. Hsieh et al. has evaluated the possibility that the EGFR gene polymorphism with the modification of the A3T bases at position 2073 of exon 21 might be a useful marker in the prediction of endometriosis susceptibility. It has been noticed that genotypes and EGFR 2073T alleles have been associated with high susceptibility for developing endometriosis and leiomyoma[25].

Antinolo et al. have evaluated the role of -403G3A and -28C3G variants situated in the promoter region of the gene, as a susceptibility factor in a group of Spanish women affected by endometriosis. No differences in the allelic frequency of either have been noticed, neither in the distribution of the haplotype/genotype among patients suffering or not suffering from endometriosis. This data shows a lack of association of these polymorphisms with endometriosis among the studied population[26].

Baxter et al have investigated a possible involvement of the TβR-I (6A) allele and the risk of cancer in a case-control study. This study has brought additional evidence regarding the association of TβR-I allele with predisposition to cancer, but it has indicated no connection of this allele with endometriosis[27].

Endometriosis is a multifactorial polygenic disease in which it seems that angiogenesis plays an important role. VEGF is a major mediator of angiogenesis and plays a key-role in the pathophysiology of endometriosis. A large number of studies have shown the existence of a role for VEGF in the progressive development of endometriosis, but individually published studies have shown the contrary. Three recent studies have shown that -406C3T and -405G3C polymorphisms of VEGF gene might be involved in the development of endometriosis in the case of certain women[28,29,30]. These polymorphisms present a great interest for future associative studies. A very recent meta-analysis has also shown that VEGF rs699947 (A>C) and rs1570360 (G>A) gene polymorphisms have been associated with a low risk for endometriosis, as they might be protective factors, while the rs3025039 (C>T) variant might determine an increased risk(31). On the other hand, it seems that VEGF receptor 2 (VEGFR-2) might be involved in the pathogenesis of endometriosis, and a recent study suggested the fact that the VEGFR-2 (1192 C/T) polymorphism might affect the risk of developing endometriosis. The authors have also studied other gene polymorphisms of VGFR-2 (1719T/A, +31C/T, IVS25-92A/G and IVS6+54C/T), without observing a statistically significant association between these and endometriosis. At the same time, a study that has investigated different mechanisms for endometriosis, such as apoptosis through the p53 codon 72 Pro-polymorphism, inflammation through the TNFα-308 polymorphism, angiogenesis through the VEGF-1154GA polymorphism, and oxidative stress through superoxide dismutase 2 polymorphisM has noticed no associations between the gene mutations of these markers and endometriosis[32,33].

Human Leucocyte Antigen System and Immune Components

An increasing number of reports suggest that endometriosis is associated with an abnormal immune function that implies changes in both cell-mediated immunity and humoral one, even though the aetiology of this disease still remains undefined[34]. It is a known fact that the human leucocyte antigen (HLA) system plays an important role in numerous diseases like diabetes mellitus or systemic lupus erythematosus[35,36].

A study carried out by Ishii et al. has evaluated a possible role played by HLA polymorphism in case of a group of women with surgically confirmed endometriosis. The authors have concluded that the incidence of the HLA-DQB1*0301 and HLA-DRB1*1403 alleles was significantly higher in patients suffering from endometriosis[37,38].

Even though the studies which have been carried out concentrated on Asian population, it can be stated that the polymorphism of the HLA system might be associated with a high risk of developing endometriosis.

3. Discussion

Up till now more than 10 million DNA sequences have been discovered in the human genome. The individual genetic variants have been nominated as a significant contributor to the aetiology of endometriosis. Some epidemiological studies suggest that endometriosis has an important family component and a number of gene polymorphisms have been associated with the clinical evolution and the susceptibility to this disease.

Gambaro et al[40] have brought into discussion the risk of hasty conclusions in the associative studies for populations, because usually, complex diseases appear through the interaction of some genetic factors with environmental factors. It is very well known that the distribution of the gene polymorphism varies among ethnic populations and represents one of the main partial factors that cast a bias over the analysis of the data referring to the involvement of polymorphisms in the pathogenesis of endometriosis[41,42,43]. This variance makes it difficult to have a general conclusion regarding

the involvement of certain gene polymorphisms in the biology of endometriosis.

The contradictory results which have been observed in this analysis indicate the fact that a single polymorphism contributes in a small proportion to the genetics of endometriosis and should be interpreted with caution, taking into consideration the large number of studies that have included only population of Asian origin. The human genome contains more than 1.8 million gene polymorphisms and the probability that one particular polymorphism might increase the risk of endometriosis is minimum[44].

4. Conclusions

In conclusion, a sole SNP presents a low probability of decisively influencing the occurrence or development of endometriosis, but certain studied polymorphic systems, such as the human leucocyte antigen, TNFα (-1031), VEGF or IL-16 systems, might present in the future a greater interest than others. However, it is clear that there is the need for some studies at a larger scale, which have to include population of different ethnicities in order to be able to explore the role played by the different gene polymorphisms or their association in the pathogenesis of endometriosis. ■

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